Pyrolytic Syntheses and Reactions of Seven-Membered Heterocycles.

By:- Lynne A. Crawford. BSc.(Hons).

Thesis presented for the degree of
Doctor of Philosophy.
University of Edinburgh.
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DECLARATION.

I declare that this thesis is my own composition, that the work which is described has been carried out by myself, unless otherwise stated, and that it has not been submitted in any previous application for a higher degree.

This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr Hamish McNab, since 1-10-98, the date of my admission as a research student.

Signed:-

Date:-

ACKNOWLEGEMENTS.

I would like to thank my supervisor Dr. Hamish McNab for his constant enthusiasm, support and advice over the last three years.

I also wish to thank the academic and technical staff at the University of Edinburgh especially Dr. D. Reed and Mr J.R.A. Millar (NMR), Mr. A Taylor (Mass spec), Mr S. Johnstone (Glassblowing) and Dr. S. Parsons (Crystallography). Thanks also to Dr. A.R. Mount and Miss M. Chapman for carrying out electrochemical experiments and for analysis of the results.

Thanks also go to the McNab Research group-past and present for all their help and for the good craic.

Special thanks go to Dr. Stuart Gebbie and Mr. Stuart Johnstone for proof-reading this manuscript. A special mention must also go to Mr. James Murphy and Mr. Iain Nicolson for helping with the writing of this thesis in their different ways.

I am grateful to my Edinburgh friends for the good times especially Ester, Isabelle, Andy, James, Graham, Dale, Iain, Ken and Stuart.

Finally, I wish to thank all my family and friends in Ireland especially Mum, Dad and Julie who have supported me constantly throughout my time in Edinburgh and without whose help I would never have written this thesis. A special mention should also go to Shauna, Alison and Clare for sharing the good times and helping me through the not so good.

I would also like to thank the EPSRC for the funding of this research.

LECTURE COURSES ATTENDED.

- Organic Research Seminars and Colloquia, Edinburgh University Chemistry Department (3 years attendance).
- Current Awareness in Organic Chemistry, Edinburgh University Chemistry Department (5 lectures, 2 years attendance).
- Royal Society of Chemistry, Perkin Division, Heterocyclic Group, Postgraduate Symposia (3 years attendance).
- Pesticides- Dr. Hamish McNab (5 lectures).
- Chemical Carcinogens- Dr. R. Michael Paton (5 lectures).
- Combinatorial Chemistry- Glaxo, SmithKline (4 lectures).
- Advanced Organic Synthesis- Dr. Alison Hulme (10 lectures).
- Royal Society of Chemistry, Perkin Division, Heterocyclic Group, Autumn Meeting, (1 years attendance).

DEDICATION.

I wish to dedicate this thesis to

Mum and Dad

for always believing in me.

ABSTRACT.

Flash vacuum pyrolysis (FVP) reactions of *N*-(4-chlorophenoxymethyl)pyridinone systems and their benzo-fused analogues were found to follow one of two pathways. The first pathway was followed by the pyridin-4-one, phenanthridinone, quinolin-2-one and quinolin-4-one systems which all gave the parent heterocycle (*i.e.* pyridine, phenanthridine or quinoline respectively). Ring-expanded azepinones were shown to be intermediates in such reactions by ^{13}C labelling experiments. The second pathway was followed by the pyridin-2-one and isocarbostyril systems where *p*-chlorophenol and the initial heterocycle (*i.e.* pyridin-2-one or isocarbostyril respectively) were obtained. The 'missing' CH_2 group was detected as ethylene by bromine trapping experiments, which suggests that these compounds act as carbene generators under pyrolytic conditions.

5-[3-(Substitutedthio)propylidene]-2,2-dimethyl-1,3-dioxan-4,6-dione derivatives were synthesised for the first time and their structures were fully analysed. When pyrolysed, these compounds did not give the expected thiepinone systems and only fragmentation products were isolated. The related 2-(alkylthio)arylmethylene precursors were also successfully synthesised but again no cyclisation products were obtained on pyrolysis. Reaction of Meldrum's acid with 2-(dialkylamino)benzaldehydes did not give the expected condensation product but instead novel 1,2,3,4-tetrahydroquinoline derivatives were obtained *via* a facile low-temperature "*tert*-amino effect."

FVP of 5*H*-dibenzo[*b,f*]azepine at 950 °C gives 9-methylacridine. However, the corresponding *N*-allylated derivative undergoes an unusual radical ring-contraction reaction to give pyrrolo[3,2,1-*jk*]carbazole; the optimum yield (63%) was obtained at 950 °C. Reactions of this pyrrolocarbazole with electrophiles (*e.g.* Vilsmeier formylation, halogenation, reaction with oxalyl chloride) gave 2-substitution products in each case.

Pyrrolo[3,2,1-*jk*]carbazole was also formed by the cyclisation of 2-(indol-1-yl)phenyl radicals generated by FVP of allyl 2-indol-1-ylbenzoates or 1-(2-nitrophenyl)indoles.

This route was found to be synthetically versatile and in optimum cases provided two-step access to substituted pyrrolo[3,2,1-*jk*]carbazoles and indolo[3,2,1-*jk*]carbazole. In some cases the reaction path was diverted to other products. Thus, when the corresponding benzimidazole and indazole systems were pyrolysed, the expected tetracycle rearranged under the reaction conditions to give 1-cyanocarbazole as the only product. FVP of the corresponding 2-methylbenzimidazole and indole systems gave 10*H*-4b,9-diazaindeno[1,2-*a*]indene and 10*H*-indolo[1,2-*a*]indole respectively; preliminary deuterium labelling experiments suggest that a hydrogen-transfer mechanism is involved. Cyclisation of the 2-(2-phenylbenzimidazol-1-yl)phenyl radical took place on the 2-phenyl substituent to give benzo[4,5]imidazo[1,2-*f*]phenanthridine rather than 1-phenyl-2,9b-diazacyclopenta[*jk*]fluorene.

CONTENTS.

1. INTRODUCTION.

1.1 Preamble.

The following introduction is in two parts and aims to review the relevant literature on the pyrolysis behaviour of seven-membered heterocycles. The first section details the literature on the synthesis of seven-membered heterocycles using pyrolytic methods and the second section details the literature on the use of seven-membered heterocycles as precursors in pyrolytic experiments. In each case, the literature is organised by the mechanism of reaction.

The synthesis section falls into eight sections.

i/ Nitrene Insertion Reactions.

ii/ Pseudo-Nitrene Insertion Reactions.

iii/ Electrocyclisation Reactions.

iv/ Apparent Nucleophilic Addition Reactions.

v/ Cycloaddition Reactions.

vi/ Retro-ene Reactions.

vii/ Radical Reactions.

The depth to which each example is examined within this review is a reflection of the data available. It should be noted that literature which postulates seven-membered rings as intermediates in pyrolysis reactions but where this ring system was not identified and characterised as an intermediate or product, is not included within the scope of this review.

1.2 Pyrolytic Methods.

Pyrolyses which are carried out in the solution phase have the disadvantage that the reactive intermediates are generated in the presence of precursor, solvent and/or products, and so complex mixtures may ensue. In addition, thermally unstable products cannot be obtained when the source of heat is present for the duration of the reaction. These problems can be partially overcome by a system where the precursor is made to flow through a tubular furnace so that individual molecules spend only a short time in the hot zone. These short contact times result in much higher reaction temperatures than are used in the solution phase and the reactions are carried out in the gas phase.

The pyrolytic methods which are used in the following review fall into three broad categories and a brief overview of the characteristics of each technique is outlined below.[1]

i/ Flow Pyrolysis

Flow pyrolysis is where the precursor is fed into a gas stream and passes through the furnace at or near atmospheric pressure. In this type of experiment the contact time of the molecules in the hot zone is of the order of tens of seconds. These long contact times mean that the furnace temperature is lower than for other pyrolytic techniques. Flow conditions are better suited to carrying out intermolecular reactions such as dimerisations or trapping reactions with an excess of reagent.

ii/ Flash Vacuum Pyrolysis

Flash vacuum pyrolysis is discussed in detail in **Section 2.1**. This is a flow system where the precursor is sublimed or distilled into the furnace under vacuum. In these reactions, the contact time for molecules in the hot zone is of the order of milliseconds. The short contact times mean that a higher furnace temperature is required in these pyrolytic reactions. This technique is best suited for carrying out intramolecular reactions.

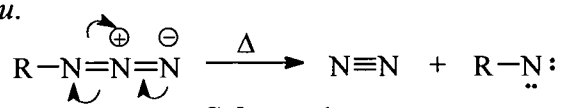
iii/ Spray Pyrolysis

Spray pyrolysis[2] is a technique that is used to carry out the gas phase pyrolysis of thermally unstable liquids or low melting solids. The method involves the introduction of the liquid directly into the furmace *via* a fine capillary in the presence of a "gentle" nitrogen flow, which ensures that the sample is injected as a fine spray. It is suited to thermally unstable or potentially explosive substrates such as azides, peroxides or diazo-compounds.

1.3 Synthesis of Seven-membered Heterocycles Using Pyrolytic Reactions.

1.3.1 Nitrene Insertion Reactions.

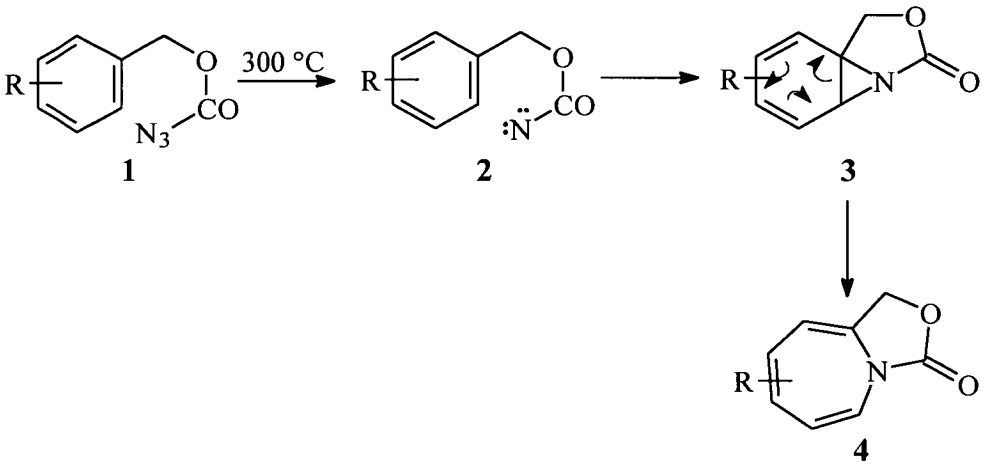
Nitrenes are the nitrogen equivalent of carbenes and are readily formed from azides. This general reaction is shown in **Scheme 1**. Nitrenes themselves are very reactive under standard conditions. They are not isolated and generally undergo further reactions *in situ*.



Scheme 1

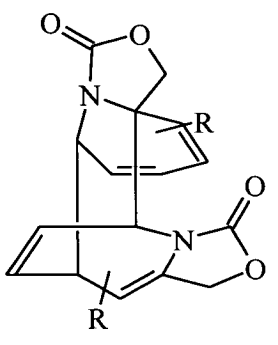
Spray pyrolysis[2] has been used to generate nitrenes from azidoformates and such nitrenes can readily add to alkenes and aromatics.

Meth-Cohn and co-workers[3, 4] have studied the spray pyrolysis reactions of benzyl azidoformates. Under pyrolysis conditions, the benzyl azidoformate **1** loses nitrogen to form nitrene **2**, this nitrene adds to the double bond of the phenyl ring to form tricyclic aziridine **3**. The ring strain of the three membered ring causes a ring-opening step to give oxazoloazepine **4**, as shown in **Scheme 2**. The ring opening in the direction of azepine formation instead of into the carbonyl containing ring follows a literature precedent.[5]



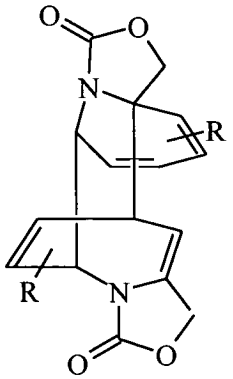
Scheme 2

These fused azepines were unstable and were only isolable when the R substituent was bulky such as 4-*tert*-butyl, mesityl (R=2,4,6-Me_3) and durenyl (R=2,3,5,6-Me_4). However, when the R substituent was less bulky such as H or Cl, the fused azepines undergo spontaneous dimerisation to form the *anti* and *syn* dimers (**5** and **6**) with no evidence of the monomeric azepine.



Anti

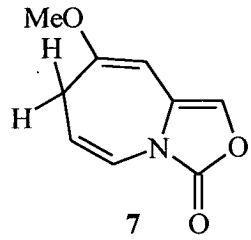
5



Syn

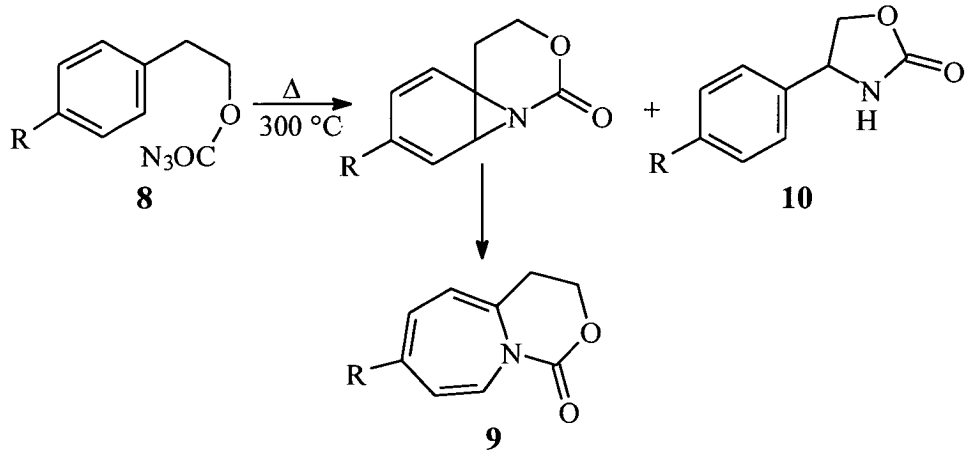
6

It should be noted that when R=3-OMe, these two dimers were formed with the rearranged azepine **7**. This azepine is formed by a hydrogen shift from azepine **4**.



7

The phenethyl azidoformates **8** behave differently on spray pyrolysis. A stable crystalline azepine **9**, which showed no tendency to dimerise or rearrange thermally was isolated in every case. The corresponding 4-aryloxazolidinone **10** was also formed in every case by nitrene insertion into the appropriate aliphatic C-H bond, with azepines being the favoured product when the R substituents were electron withdrawing groups. The general reaction is shown in **Scheme 3**, with the substituents and corresponding product yields in **Table 1**.



8 **10**

9

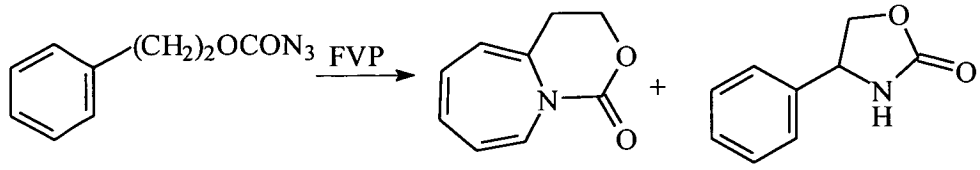
Scheme 3

R	MeO	Bu^t	Me	Cl	Br	CN	NO_2
9	61	56	54	38	20	0	0
10	10	12	19	22	18	trace	0

Table 1- Yields of compounds **9** and **10** with different R substituents.

The information in **Table 1** shows that both products were obtained except when the R group was the nitro or the cyano group and no products were isolated from these pyrolysis reactions.

Abramovitch and co-workers[6] subjected compound **11** to FVP conditions at 650 °C and this resulted in compounds **12** and **13** in yields of 26% and 40% respectively. The general reaction is shown in **Scheme 4**.

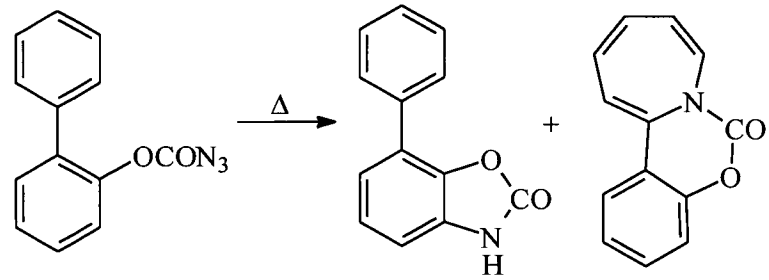


11 **12** **13**

Scheme 4

This work is similar to the spray pyrolysis reactions carried out by Meth-Cohn and co-workers which are described above. The spray pyrolysis reactions occur at the lower temperature of 300 °C with the azepine the major product. Under FVP conditions the temperature required for the reaction is 650 °C with the azepine being the minor product. A direct comparison cannot be made as Abramovitch synthesised only the parent system **12** and Meth-Cohn only the substituted heterocycles **9**.

Meth-Cohn and co-workers[7] investigated the spray pyrolysis behaviour of arylazidoformates. The pyrolysis behaviour of biphenyl-2-yl azidoformate **14** is shown in **Scheme 5**.



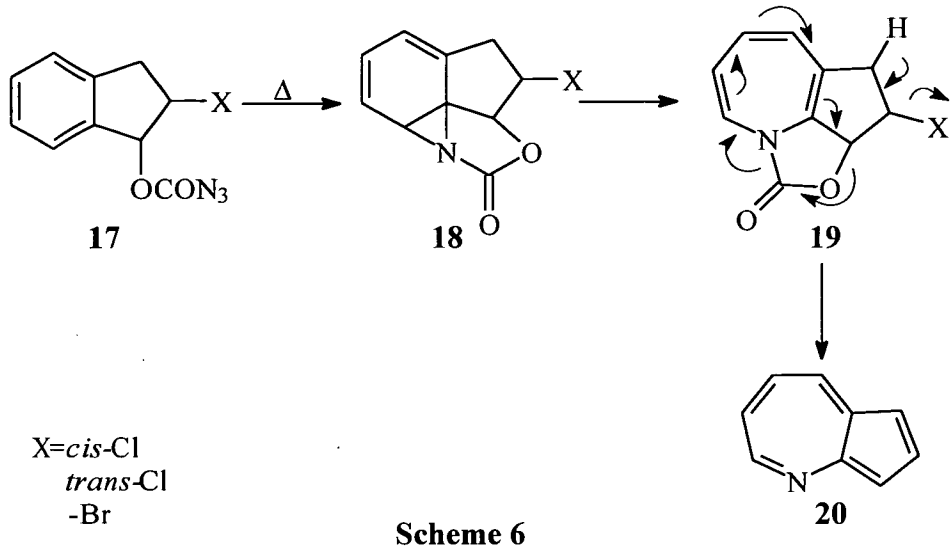
14 **15** **16**

Scheme 5

Compound **14** has two potential sites for nitrene attack, the vacant *ortho*-position to give **15** and the 1,2 bond of the phenyl substituent to give **16**. Both these products were formed in 24% and 46% yield respectively.

In an extension to this work, similar precursors were used in the generation of 7,5-fused products. Meth-Cohn and co-workers[8, 9] have synthesised the unstable unsubstituted aza-azulenes with nitrogen in the seven-membered ring. The general reaction pathway is shown in **Scheme 6**. Spray pyrolysis of the azidoformate **17** generates, with the loss of nitrogen, the nitrene which adds to the aryl group to give

tetracyclic structure **18**. This three membered ring opens to give intermediate **19**. Loss of carbon dioxide and HX results in the aza-azulene **20**.

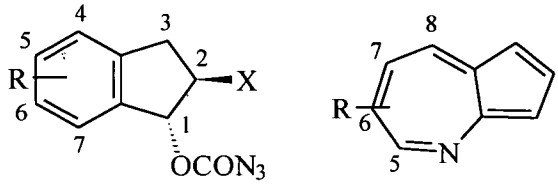


X=*cis*-Cl
trans-Cl
-Br

Scheme 6

A halide atom was used as the X-substituent as it was capable of blocking attack of the nitrene at this alternative site of attack and it could be eliminated as HX to allow the intermediate hydroaza-azulene to be at the correct oxidation level for aromatisation to take place. The aza-azulene **20** was produced directly in good yield, irrespective of the halogen atom or its stereochemistry. It should be noted that the pyrolysis tube was packed with copper turnings and calcium oxide chips so that the eliminated hydrogen halide could be absorbed, otherwise poor yields were obtained.

This work was then extended to investigate the pyrolysis reactions of substituted *trans*-2-bromoindan-1-yl azidoformates **21**.

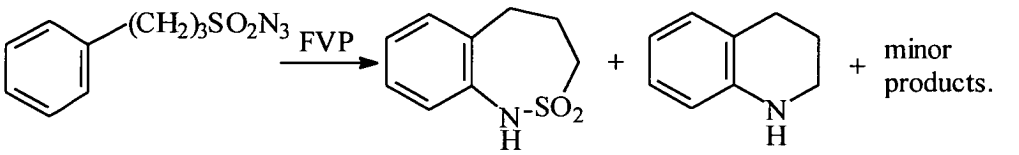


21a; R=5-Br X=Br **22a**; R=7-Br
21b; R=6-OMe X=Br **22b**; R=6-OMe
21c; R=5-Br X=H

The dibromoazidoformate **21a** resulted in 7-bromoazulene **22a** in 30% yield, with no evidence of loss of the bromide on the phenyl ring. The 5-bromoindan-1-yl azidoformate **21c** gave compound **20** in 10% yield after pyrolysis. The authors suggest that this is due to a more energetically demanding elimination, after suitable H-shifts, of hydrogen bromide. The 6-methoxy derivative **21b** resulted in

6-methoxy-4-aza-azulene **22b** in 50% yield. However, the electron donating nature of the methoxy group did not stabilise the aza-azulene system as expected and this product was more prone to degradation than the parent system.

Abramovitch and co-workers[6] have studied the flash vacuum pyrolysis of substituted sulfonyl azides as shown in **Scheme 7**.



23 **24** **25**

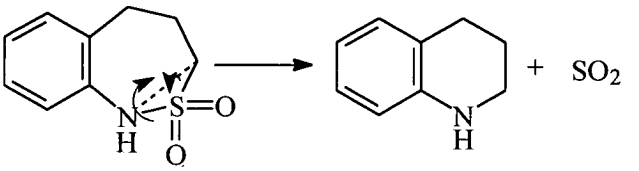
Scheme 7

The pyrolysis of 3-phenyl-1-propane-sulfonyl azide was carried out at 360, 650 and again at 990 °C and the product yields are shown in **Table 2**.

Temperature/°C	Compound **24** yield	Compound **25** yield	Other product yield
360	27%	5.3%	~5%
650	7.5%	60.3%	trace
990	0.4%	72.4%	25%

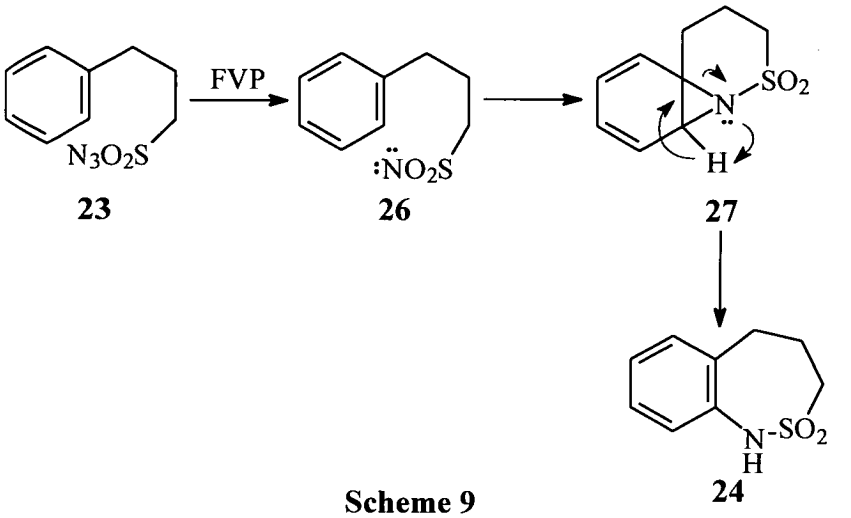
Table 2-The yields for pyrolysis products of compound **23** at various temperatures.

This information suggests that lower temperatures favour the formation of the seven-membered ring product, **24**. Therefore at higher temperatures compound **25** appears in much higher yields, and it should be noted that compound **25** can be formed by the extrusion of SO_2 from compound **24**. This suggests that compound **24** is unstable under the more extreme temperatures in the FVP experiments. The proposed mechanism for this extrusion is shown in **Scheme 8**.



Scheme 8

The proposed mechanism for sulfonylnitrene insertion is shown in **Scheme 9**.

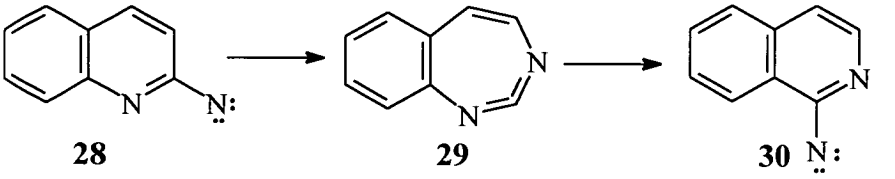


23 **26** **27** **24**

Scheme 9

The nitrene **26** inserts into the phenyl ring to give tricyclic compound **27** which undergoes a ring opening and hydrogen shift to give product **24**. In this case, however, the ring opening step follows a different direction to those described previously in **Schemes 3** and **4**. There is a literature precedent for this ring opening following the direction indicated above and it is thought this is due to the greater stability of the developing sulfonamide derivative.[10]

Wentrup and co-workers[11] have carried out extensive studies on the behaviour of nitrenes under pyrolysis conditions. In proposed mechanisms for these studies, they formulated that seven-membered rings were likely intermediates.[12] An example is shown in **Scheme 10**.



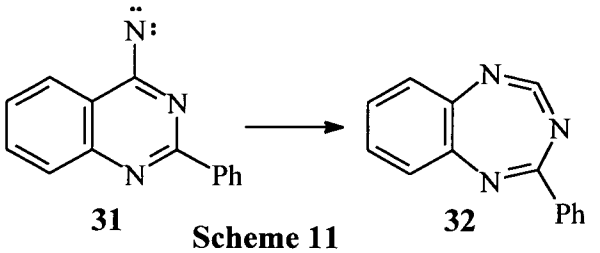
28 **29** **30**

Scheme 10

However, carbodiimide intermediates such as compound **29** which can be formed by nitrene insertion of compound **28**, are unstable and are therefore not observed under standard pyrolysis conditions. Therefore a specialised system has to be employed if these intermediates are to be identified and characterised.

Wentrup and co-workers carried out their flash vacuum pyrolysis reactions in a matrix isolation apparatus that allowed the direct infrared spectroscopic observation of the products at -196 °C.

In one example, compound **31** resulted in compound **32**.

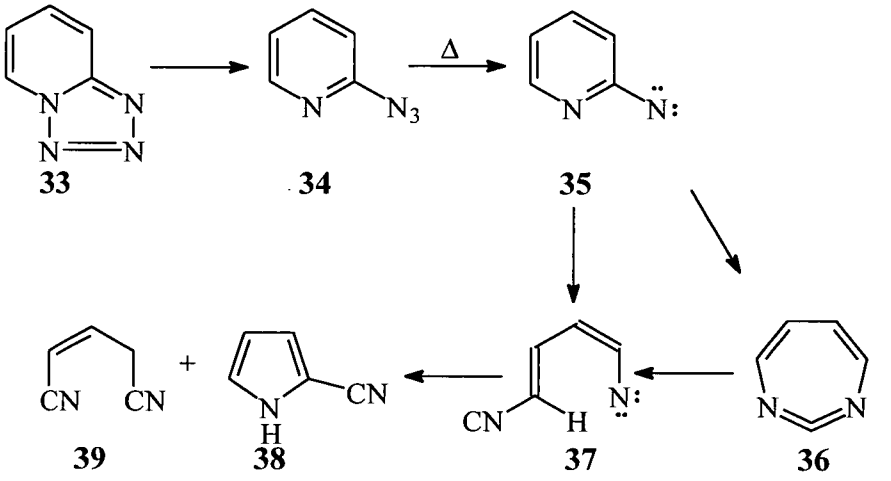


31 **32**

Scheme 11

It is thought that nitrene **31** undergoes a ring expansion reaction to give compound **32** and this compound was identified by matrix-isolation techniques in argon at -196 °C. It should be noted that IR signals due to **32** disappeared when the matrix was heated to -70 °C.

This work was extended and the pyrolysis behaviour of compound **33** was investigated. The general reaction is shown in **Scheme 12**.



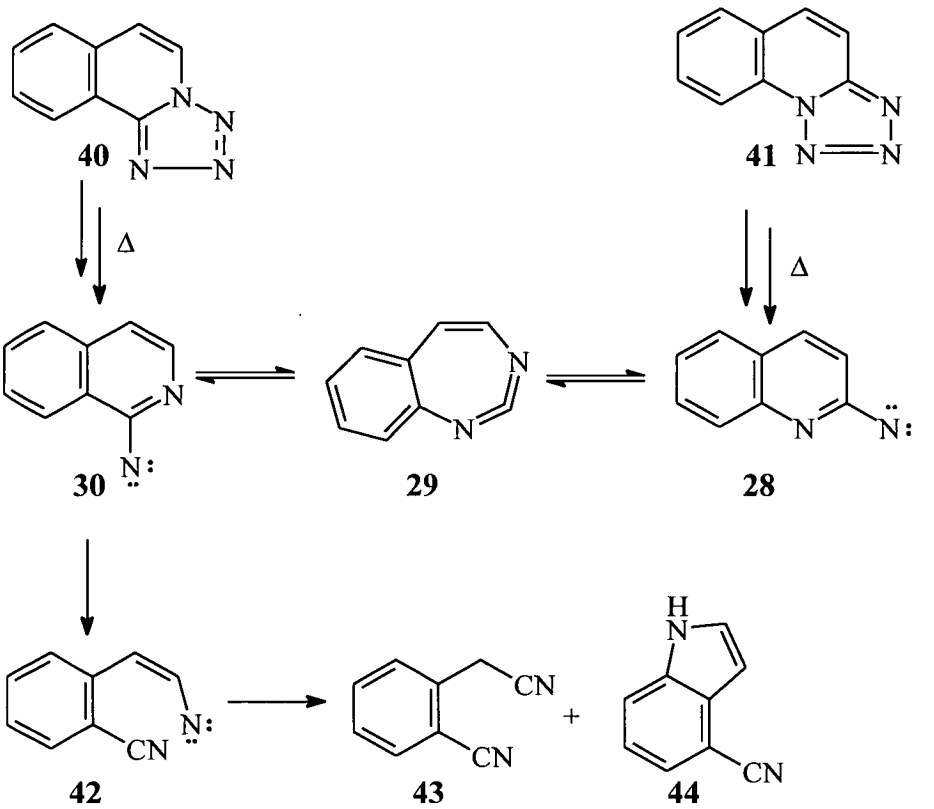
33 **34** **35** **36** **37** **38** **39**

Scheme 12

Sublimation of compound **33** through the FVP apparatus at 150 - 200 °C caused the complete transformation into azide **34**. This was confirmed by the azide absorptions (at 2300 and 2420 cm^{-1}) on the infrared spectrum. When the pyrolysis was carried out at 480 °C, azide **34** was still present along with an absorption due to the 2-cyanopyrrole **38** and a sharp band at 1975 cm^{-1} which was identified as carbodiimide **36**. However when warmed to room temperature, the only products were **38** and **39**, formed *via* intermediate **37**, which is not surprising due to the unstable nature of the carbodiimide.[13, 14] When the pyrolysis was carried out at 370 °C, both **34** and **36** were formed with the two cyano products **38** and **39** absent from

the pyrolysate. However at higher pyrolysis temperatures, there was increased formation of the cyano products with a gradual disappearance of carbodiimide **36**.

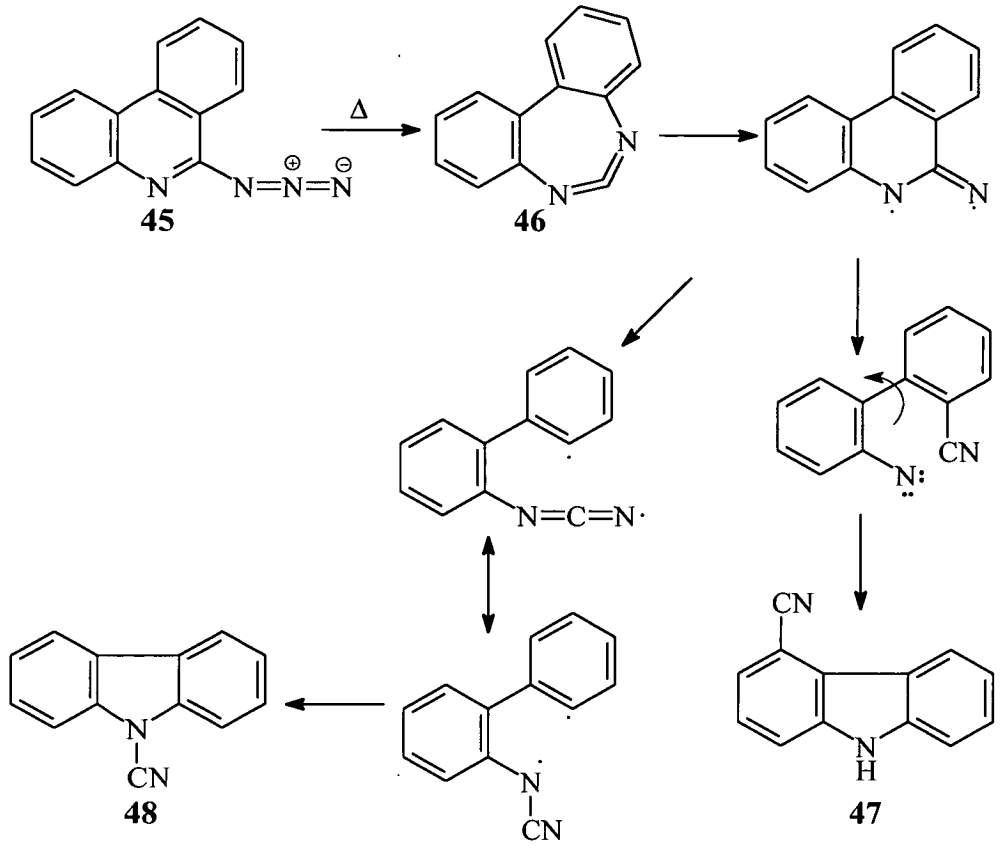
The presence of this carbodiimide intermediate was further confirmed by the observation of a common intermediate **29** in the pyrolyses of tetrazolo[5,1-*a*]isoquinoline **40** and tetrazolo[1,5-*a*]quinoline **41**, as shown in **Scheme 13**.



Scheme 13

At a pyrolysis temperature of 380 °C, a signal due to carbodiimide **29** appeared on the infrared spectrum which gradually disappeared at pyrolysis temperatures of 500 °C and above, to be replaced by signals due to cyano compounds **43** and **44**.

Since annelated benzene rings appeared to stabilise the cyclic carbodiimides, compound **45** was also investigated. The general reaction is shown in **Scheme 14**.

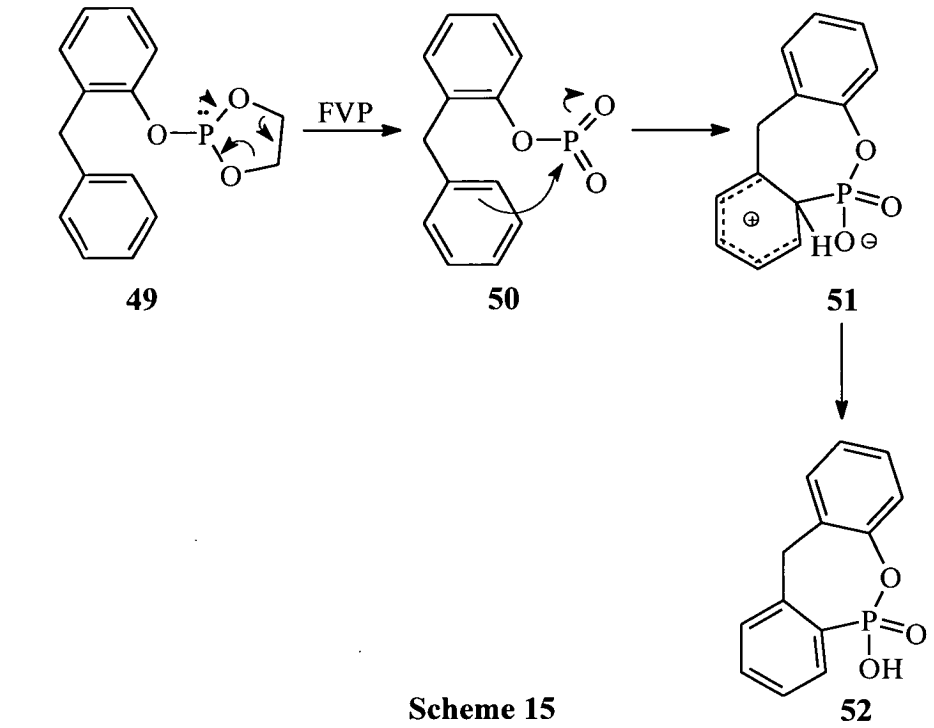


Scheme 14

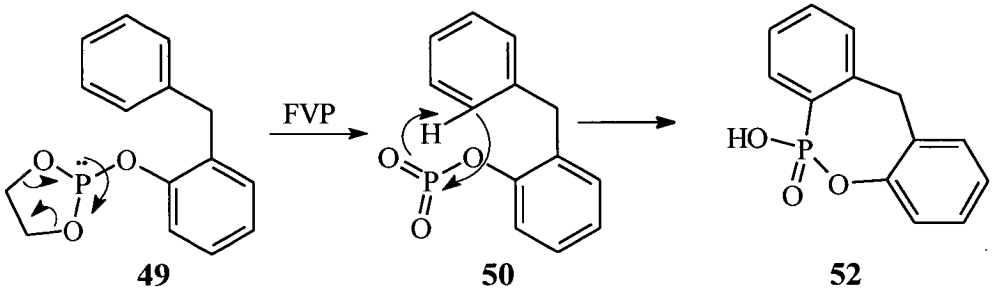
When pyrolysed at 490 °C, the signal due to azide **45** completely disappeared on the infrared spectrum and an almost pure sample of carbodiimide **46** was obtained, which was again identified by a strong absorption in the infrared spectrum. At higher temperatures (700 – 800 °C), pyrolysis of compound **45** resulted in the formation of 4- and 9-cyanocarbazole,[12, 15] **47** and **48**.

1.3.2 Pseudo-Nitrene Insertion Reactions.

Cadogan and co-workers[16, 17] have subjected compound **49** to flash vacuum pyrolysis conditions at 700 °C. This resulted in compound **52** in 45% yield. The authors suggest the mechanism for this reaction is as shown in **Scheme 15**. When compound **49** was pyrolysed, it resulted in the metaphosphate moiety **50** by the thermal elimination of ethylene. The phenyl ring then attacks the phosphorus to give a Wheland type intermediate **51**, which rearranges to give product **52**. However, electrophilic addition reactions of this type are rare in the gas phase and it seems more likely that the reaction occurs by a mechanism such as that shown in **Scheme 16**.



Scheme 15

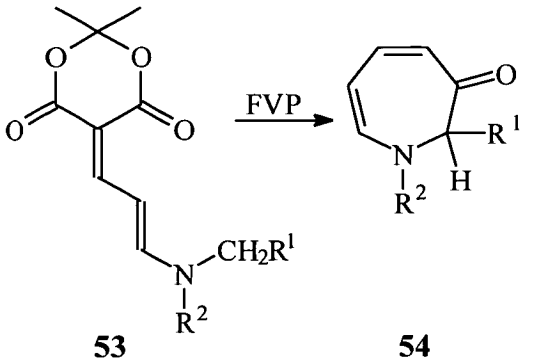


Scheme 16

It is proposed that the metaphosphate moiety **50** is produced and this inserts into the other phenyl ring in a similar manner to nitrene insertion reactions, to give compound **52**.

1.3.3 Electrocyclisation Reactions.

The synthesis and reactions of 1*H*-azepin-3-ones have been studied in depth by McNab and co-workers[18, 19] and they found that the flash vacuum pyrolysis of Meldrum's acid derivatives **53** led to the formation of azepinones **54**, in yields of 64 - 75%. These pyrolysis reactions were carried out at 500 °C. A variety of derivatives were synthesised, as shown in **Scheme 17**.



53 **54**

a; R^1=H, R^2=Me, Ph or Pr^i

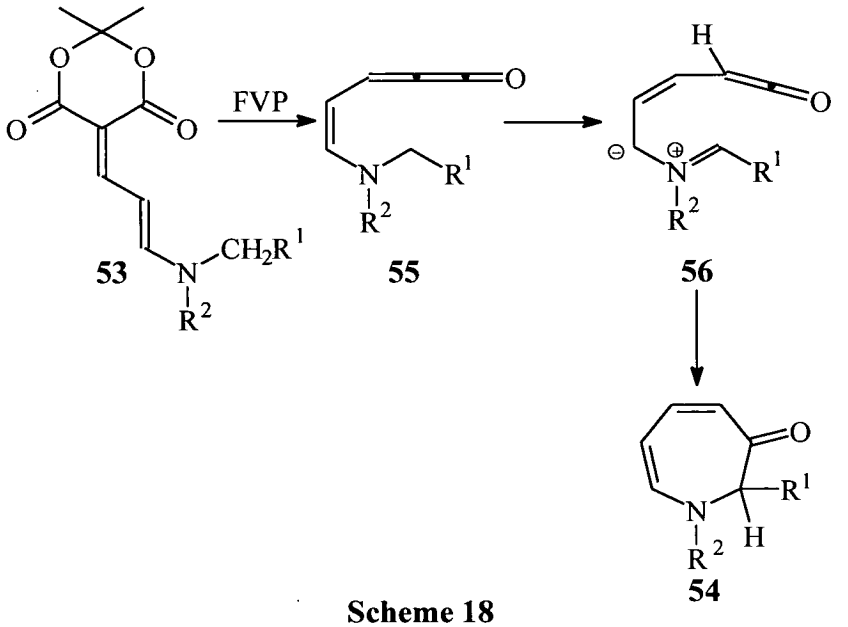
b; R^1=Me, R^2=Et

c; R^1=R^2=Ph

d; R^1=Me, R^2=Ph

Scheme 17

The derivatives **53a**, **53b**, **53c** and **53d** show that this cyclisation can take place at *N*-methyl, *N*-methylene and *N*-methine groups which result in 1-substituted, 1,2-disubstituted and 1,2,2-trisubstituted azepinones **54a**, **54b**, **54c** and **54d** respectively, although in a competitive case there is little regioselectivity. The formation of the azepinone can be rationalised in terms of an electrocyclisation reaction as shown in **Scheme 18**.

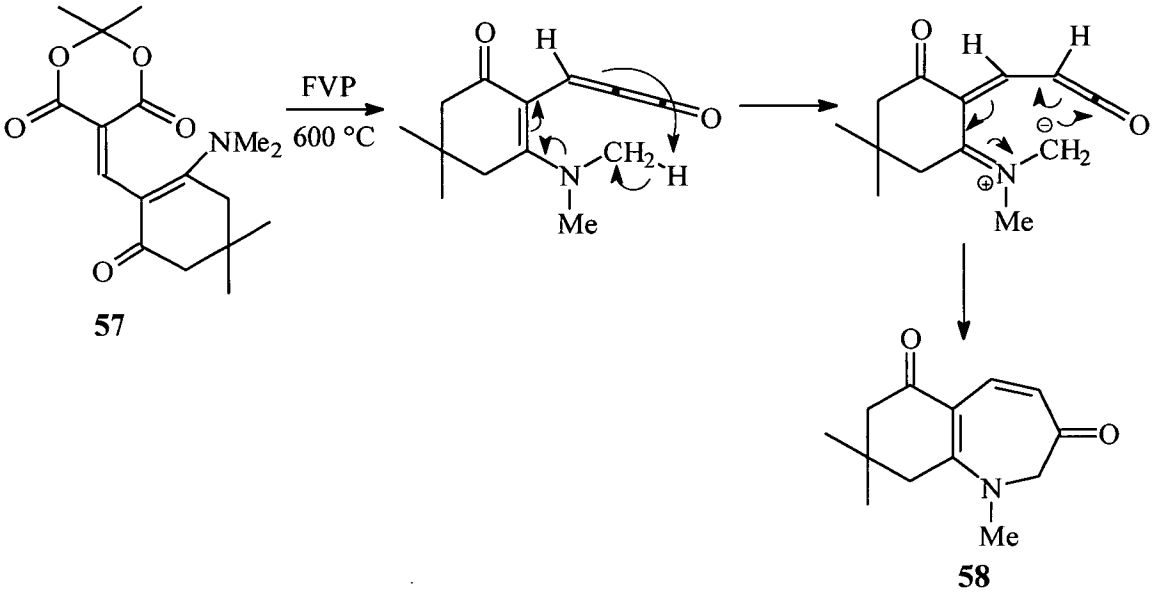


53 **55** **56** **54**

Scheme 18

During the pyrolysis, the Meldrum's acid ring collapses with the loss of acetone and carbon dioxide to give the methyleneketene intermediate **55**. Hydrogen transfer in this intermediate leads to the 1,7-dipolar intermediate **56**. This collapses *via* an electrocyclisation reaction to the azepinone **54**. It should be noted that this pyrolytic route is the only general synthesis of 1*H*-azepin-3(2*H*)-ones.

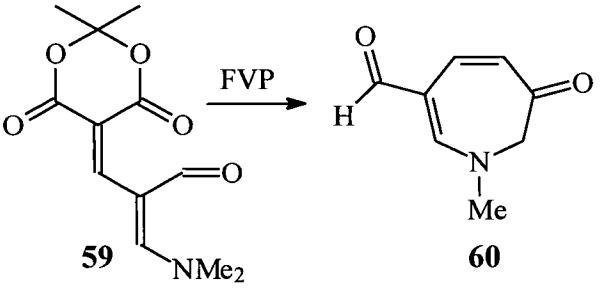
There are some further examples of seven-membered heterocycle formation following a similar hydrogen shift-electrocyclisation reaction mechanism and one example is illustrated in **Scheme 19**. McNab and co-workers[20] pyrolysed compound **57** which resulted in the fused azepinone **58** in 45% yield.



57 **58**

Scheme 19

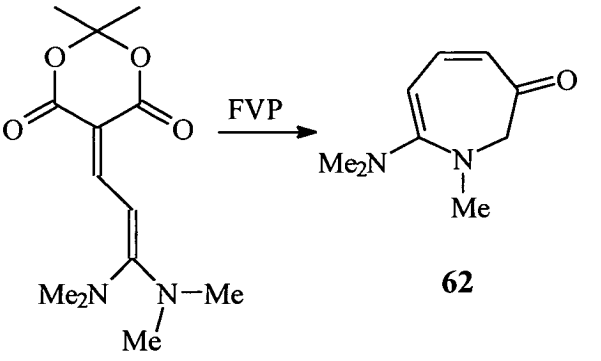
A second example is shown in **Scheme 20**. A small scale pyrolysis of compound **59** gave a product that was tentatively identified as compound **60**, but there was insufficient material for full characterisation to be carried out.



59 **60**

Scheme 20

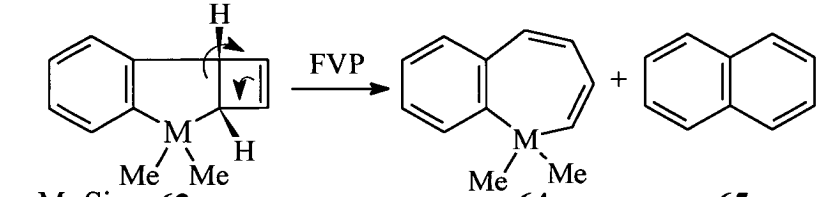
McNab and co-workers[21] then investigated the incorporation of a strong electron-donating group in the 7-position of the azepinone which substantially modifies the electron distribution in the conjugated system of these heterocycles. Compound **61** was subjected to FVP conditions at 600 °C and resulted in azepinone **62** in 90% yield, as shown in **Scheme 21**.



61 **62**

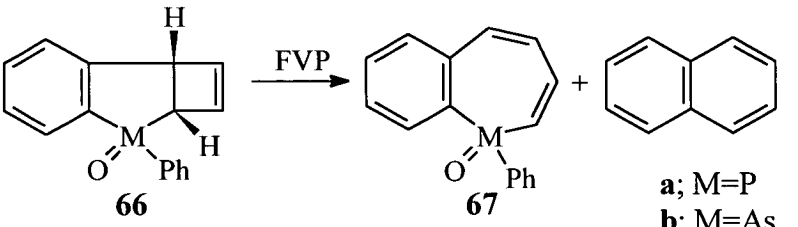
Scheme 21

Tsuchiya and co-workers[22, 23] have used FVP in the synthesis of novel benzoheterepine systems with unusual heteroatoms, as outlined in **Schemes 22** and **23**. In each case, naphthalene is formed as a side product and comes from the extrusion of the heteroatom and its substituents from the seven membered ring. It is thought that these compounds are formed by an electrocyclisation with ring opening reaction, as shown in **Scheme 22**. It is noted that the authors have not discussed the stereochemistry involved in this reaction but this transformation is symmetry allowed thermally and therefore should occur in a conrotatory manner.



a; M=Si **63** **64** **65**
b; M=Ge

Scheme 22



66 **67**

a; M=P
b; M=As

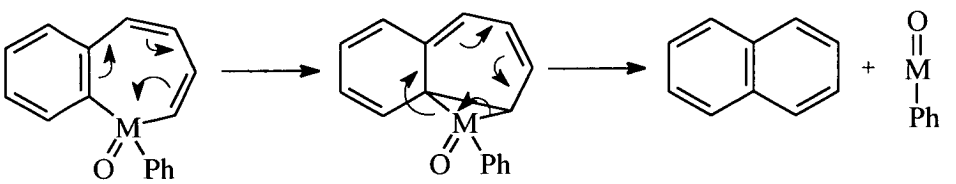
Scheme 23

The pyrolysis of compounds **63a**, **63b** and **66b** was carried out at a number of temperatures and the relative yields of each product at these temperatures are shown in **Table 3**.

M	Temperature /°C	Yield **64** or **67**	Yield **65**
Si; **63a**	450	59	Trace
	500	84	12
	550	77	21
Ge; **63b**	450	33	15
	500	47	42
	550	15	83
As; **66b**	500	40	31
	530	39	42
	550	27	49

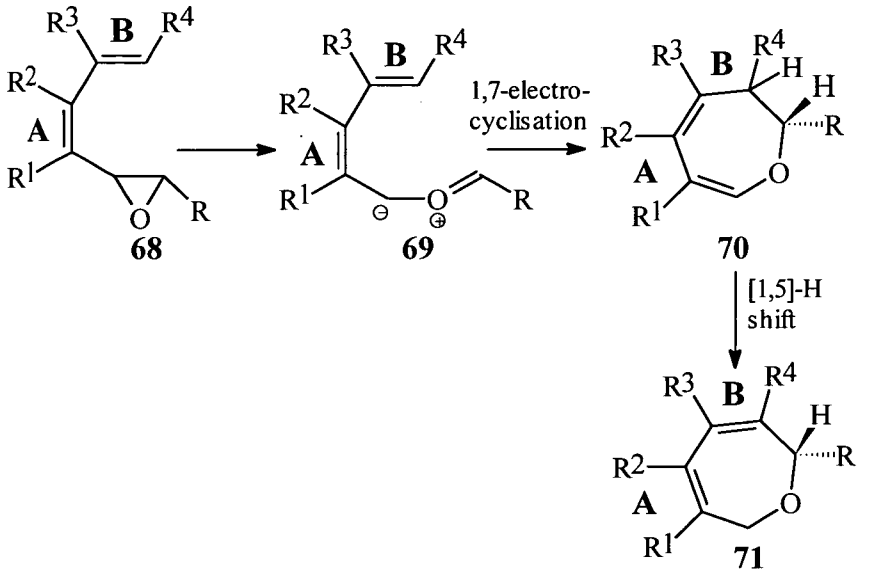
Table 3-Yields for pyrolysis of compounds **63a**, **63b** and **66b** at varying temperatures.

These results suggest that 500 °C seems to be the optimum temperature for the syntheses of these compounds. As the pyrolysis temperature increases, the proportion of naphthalene **65** in the pyrolysate increases which suggests that the seven-membered rings are more prone to extruding the heteroatom at these temperatures. In the case of compound **66a**, a pyrolysis temperature of 550 °C was used which resulted in compound **67a** in 85% yield with naphthalene **65** in 5% yield. The proposed mechanism for this extrusion is shown in **Scheme 24**.



Scheme 24

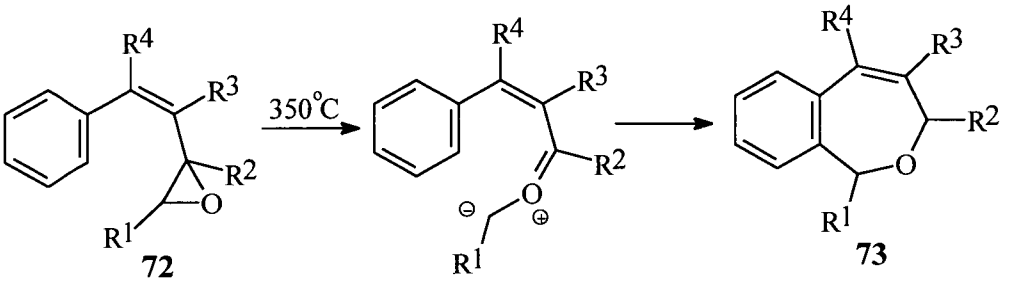
The Eberbach and Sharp groups have carried out extensive work on the cyclisation of diene-conjugated carbonyl ylides **69** with various types of unsaturated systems at the A and B positions or with different substituents at positions R^1, R^2, R^3 and R^4. The general reaction is shown in **Scheme 25**.[24, 25, 26]



Scheme 25

Carbonyl ylide **69** can be generated by the thermal conrotatory ring opening of oxiranes. These species undergo a formally conrotatory 1,7-electrocyclisation reaction to give the intermediate **70** which then rearranges by an *in-situ* [1,5] sigmatropic hydrogen shift to give the isolated products **71**. It should be noted that the stereochemistry at the carbon with R^4 will be lost when the final hydrogen shift takes place.

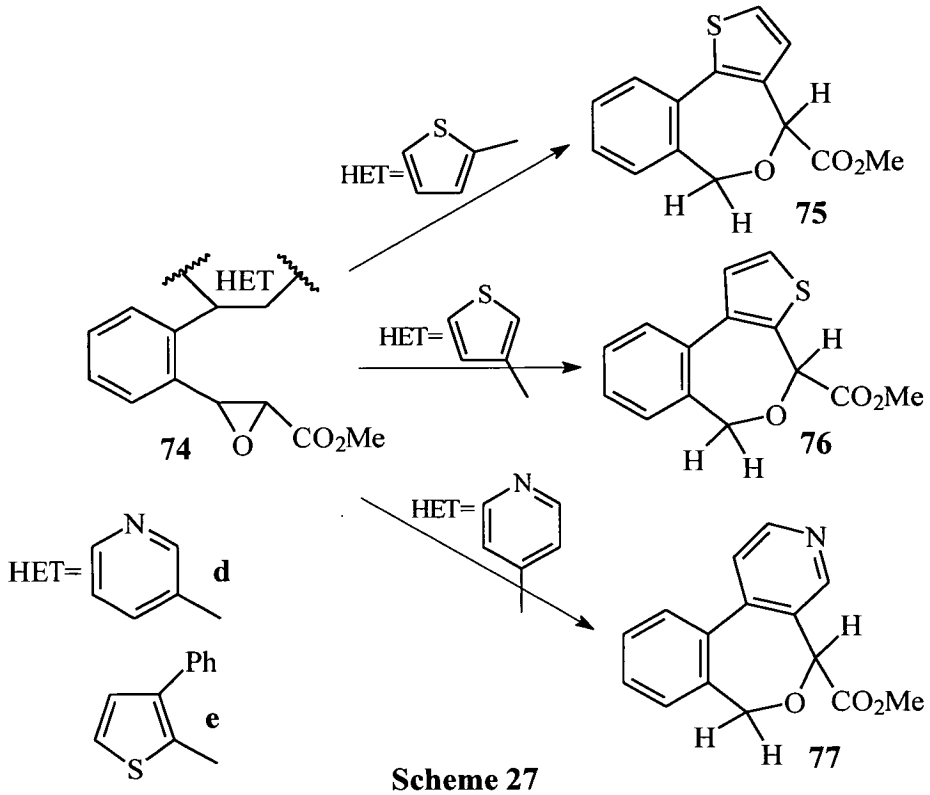
Eberbach and co-workers[25] used flow pyrolysis conditions at 350 - 390 °C to yield compounds **73a**, **73b** and **73c** from the appropriately substituted (Z)-styryloxiranes **72a**, **72b** and **72c**. These were prepared in yields of 55%, 70% and 80% respectively. This is shown in **Scheme 26**.



a; R^1=CO_2Me, R^2=H, R^3=CO_2Me, R^4=H
b; R^1=CO_2Me, R^2=H, R^3=H, R^4=Ph
c; R^1=Ph, R^2,R^3=-$(CH_2)_4$-, R^4=H

Scheme 26

Sharp and co-workers[26] extended this work to investigate the effects of substituents on the benzene ring under attack and the relative reactivity of the other heterocyclic rings at the B position (**Scheme 25**) under flash vacuum pyrolysis conditions. The different systems synthesised are shown in **Scheme 27**.

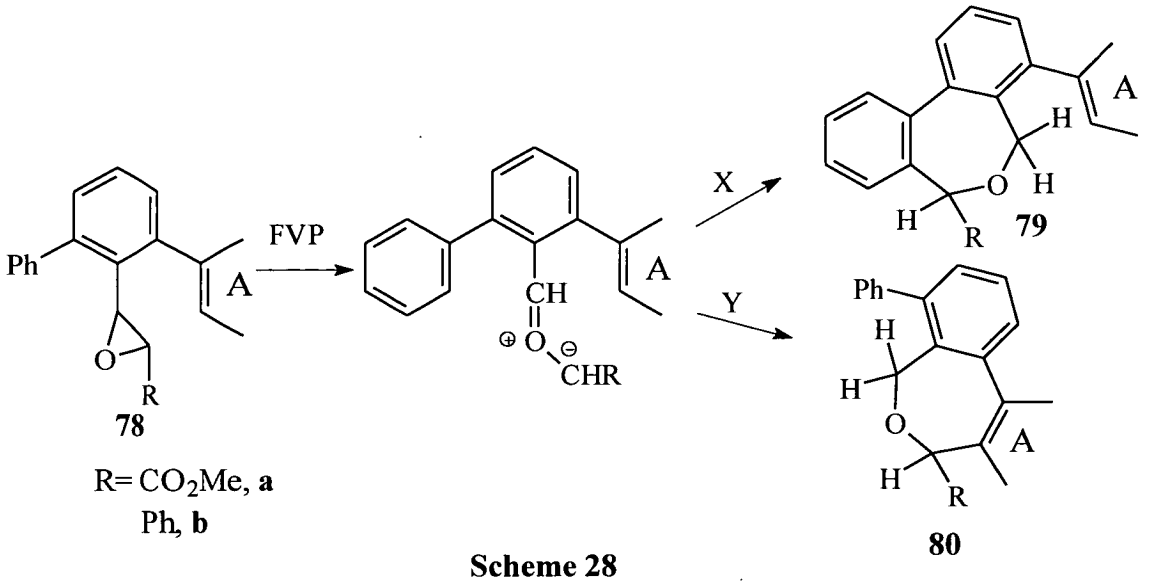


Scheme 27

All the precursors were pyrolysed at 625 °C and gave compounds **75**, **76** and **77** in 80%, 76% and 56% yield respectively. The other two precursors **74d** and **74e** polymerised to give a black tar on distillation into the furnace tube from which no products were obtained.

These results show that the 1,7-electrocyclisation reactions of carbonyl ylides provide a route to heterofused dihydrobenzoxepines irrespective of whether the heterocyclic ring under attack is electron rich or electron poor.

Sharp and co-workers[27] then extended this work by carrying out a series of experiments in which the carbonyl ylide obtained from the pyrolysis of compound **78a** and **78b**, can cyclise *via* two different pathways. If pathway "X" is followed, it cyclises onto the unsubstituted phenyl group at the 2-position to give compound **79** but if pathway "Y" is followed, then the ylide can cyclise onto the substituent at the 6-position to give compound **80**.



R= CO_2Me, **a**
Ph, **b**

Scheme 28

The ratio of products **79**:**80** were measured when a variety of unsaturated substituents were used as the A group (incorporated at the 6-position, relative to that of the phenyl group in the 2-position). The product ratios and yields for these pyrolysis reactions are contained in **Table 4**.

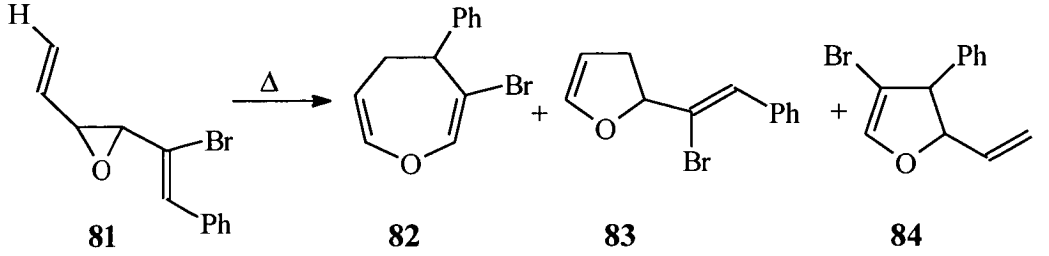
A Substituent	**80a**:**79a**	Yield/%	**80b**:**79b**	Yield/%
(E)-2-phenylethenyl	20	65	-	-
2-thienyl	9	70	-	-
3-thienyl	8	75	-	-
3,5-dichlorophenyl	1.5	75	-	-
3,5-bis(trifluoromethyl)phenyl	0.7	70	0.7	75
3,5-dimethylphenyl	0.8	70	0.9	75
3-nitrophenyl	1.3	70	-	-
4-fluorophenyl	1.2	70	-	-
4-methylphenyl	1.3	75	-	-
4-chlorophenyl	1.2	70	-	-
4-methoxyphenyl	1.2	75	-	-
4-(trifluoromethyl)phenyl	1.3	86	-	-

Table 4- Yields and product ratio for the pyrolysis reaction of compound **78**.

The results in **Table 4** show that substituent R has no effect on either the yield or the ratio of products **80**:**79**. When R=CO_2Me, the isomer ratio seems to remain fairly constant for most A substituents, ranging from 0.7 – 1.5. However, when the A group is 3-thienyl, 2-thienyl and (E)-2-phenylethenyl, the ratio varies to 8, 9 and 20 respectively showing a strong preference for compound **80**. The authors suggest that this can be attributed to the increasing double bond character associated with each

group and the cyclisations follow the expected order of reactivity-benzene<thiophene<olefin.

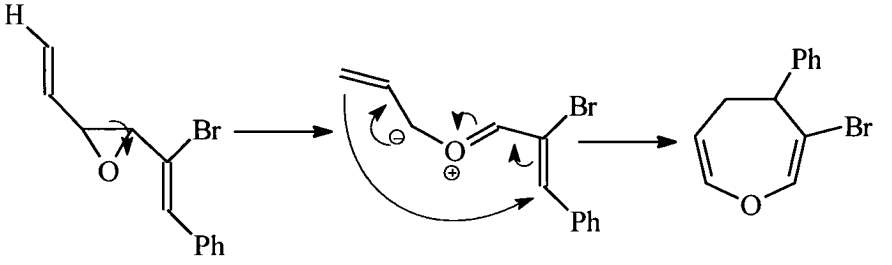
Chuche and co-workers[28] have also subjected substituted three-membered rings to pyrolysis conditions. In one example outlined in **Scheme 29**, the *trans* epoxide **81** rearranged at temperatures of 360 °C and compound **82** was isolated along with two dihydrofurans, **83** and **84**. This was carried out under flow pyrolysis conditions, where the precursor in cyclohexane was passed through a vertical tube filled with glass balls.



81 **82** **83** **84**

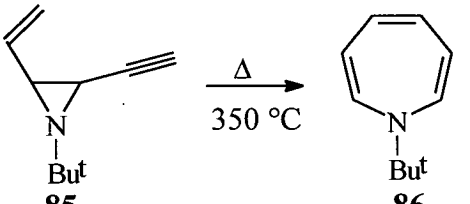
Scheme 29

Dihydrofurans **83** and **84** are formed from participation of the two vinyl groups and compound **82** is formed by the thermal ring opening of the oxiranes followed by a 1,7 electrocyclisation reaction. This is shown in **Scheme 30**.



Scheme 30

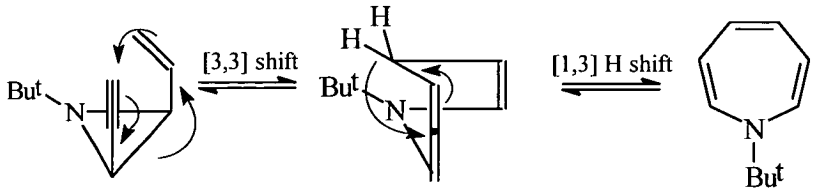
A second example was also carried out under flow pyrolysis conditions where the *cis* 1-ethynyl-2-vinyl-oxirane **85** was dropped through a hot vertical tube held at 15 Torr. This resulted in azepine **86** in high yield, as shown in **Scheme 31**.[29, 30]



85 **86**

Scheme 31

The proposed mechanism is shown in **Scheme 32**

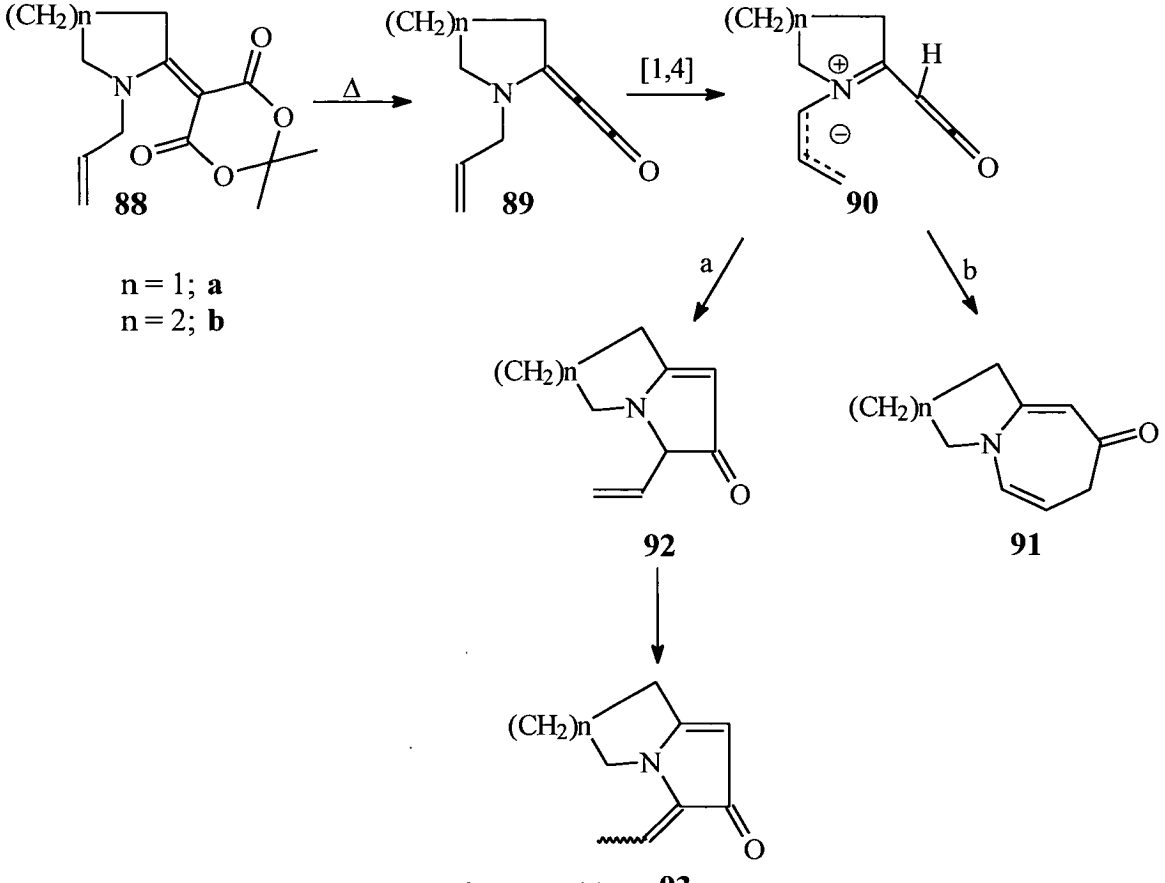


85 **87** **86**

Scheme 32

In the first step, a highly strained seven-membered intermediate **87** is formed *via* a [3,3] sigmatropic rearrangement. The authors suggest that the azepine **86** is formed by a [1,3] hydrogen shift although this is forbidden thermally by the Woodward-Hoffman rules. A recent review by McNab and co-workers[31] suggests that such shifts may occur with low activation energy as strained structures such as **87** possess a low energy LUMO in the plane of the molecules.

Chuche and co-workers[32] have investigated the behaviour of compounds **88a** and **88b** under flash vacuum pyrolysis conditions and have found that these reactions result in the formation of compounds **91** and **93**, as shown in **Scheme 33**.



88 **89** **90**

n = 1; **a**
n = 2; **b**

92 **91**

93

Scheme 33

Flash vacuum pyrolysis of compound **88** produces methyleneketene **89** with loss of acetone and carbon dioxide. This can undergo a [1,4] hydrogen shift to the dipolar intermediate **90** which can in turn, undergo one of two electrocyclisation reactions. If pathway "a" is followed then intermediate **92** would be formed and would rearrange to the more stable conjugated product **93**. If pathway "b" is followed, the azepinone **91** would be formed.

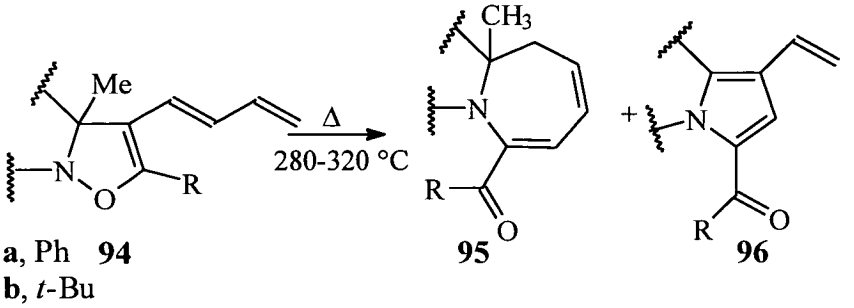
The ratio of products formed seems to be temperature dependent and the results are shown in **Table 5**.

Compound	Temperature/°C	Ratio **93** : **91**
88a	470	1:4
	580	1:1
88b	490	1:1
	680	20:1

Table 5-The ratio of products **93**:**91** at varying temperatures.

Pyrrole system **88a** seems to favour the azepinone **91** at the lower temperature of 470 °C but there seems to be an equal distribution of products **91** and **93** at the higher temperature of 580 °C. The piperidine system **88b** seems to have an equal distribution of compounds **93** and **91** at the lower temperature of 490 °C but compound **93** is favoured greatly at the higher pyrolysis temperature of 680 °C.

Other studies by Eberbach and co-workers[33] reported the formation of bicyclic azepines from 2,3-dihydroisoxazoles using pyrolysis reactions. These are carried by dropping a solution of the precursor in benzene through a hot vertical tube in a stream of nitrogen and the general reaction is shown in **Scheme 34**.



a, Ph **94**
b, *t*-Bu

95 **96**

Scheme 34

The cyclic derivatives with the yields of each product are shown in **Table 6**.

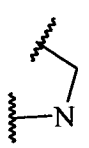
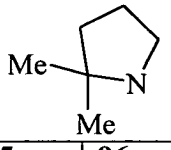
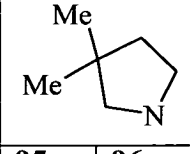
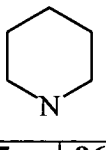
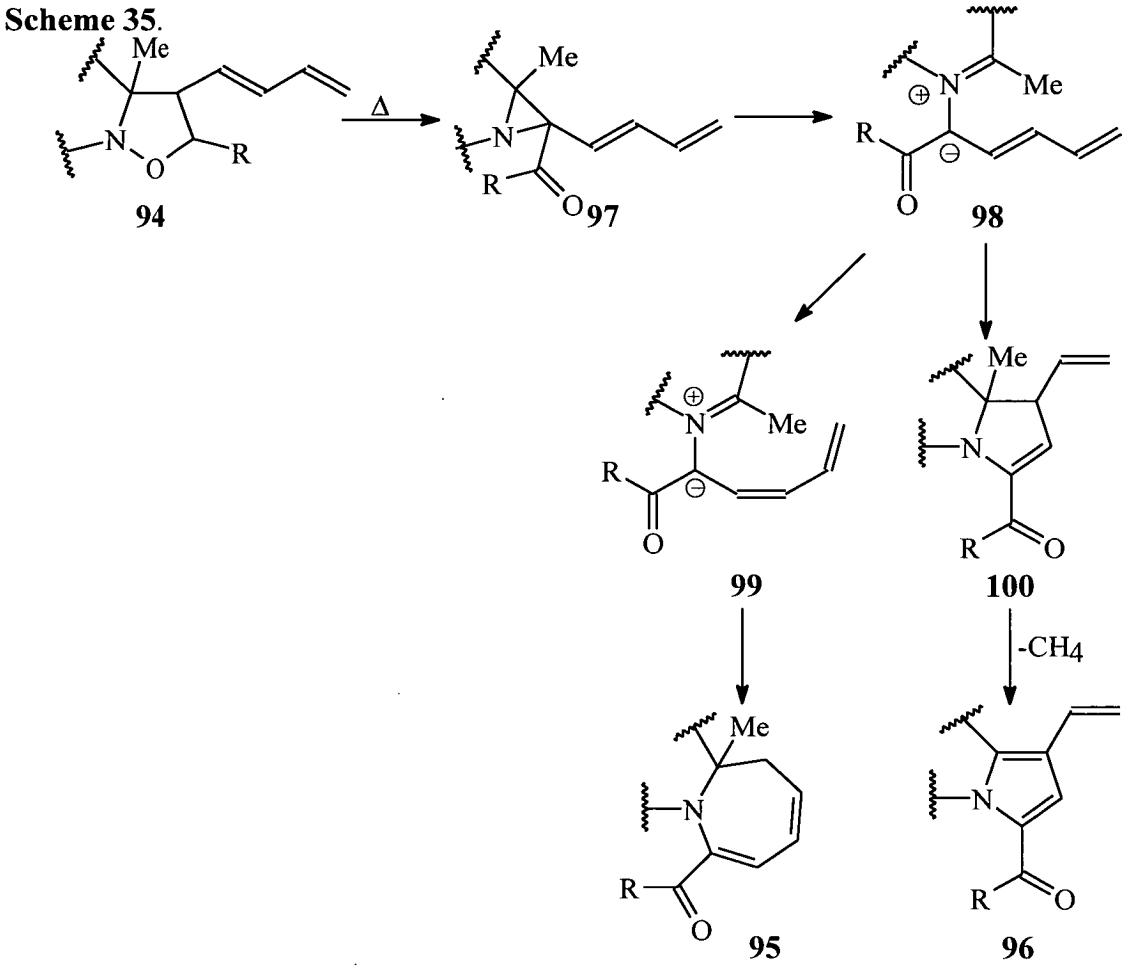
						
	95	**96**	**95**	**96**	**95**	**96**
a	59	9	48	3	42	7
b	13	-	38	trace	41	trace

Table 6:- The yields and derivatives used in the pyrolysis of compound **94**.

This information suggests that the azepine is the major product in every case. The formation of these products has been rationalised mechanistically, as shown in **Scheme 35**.

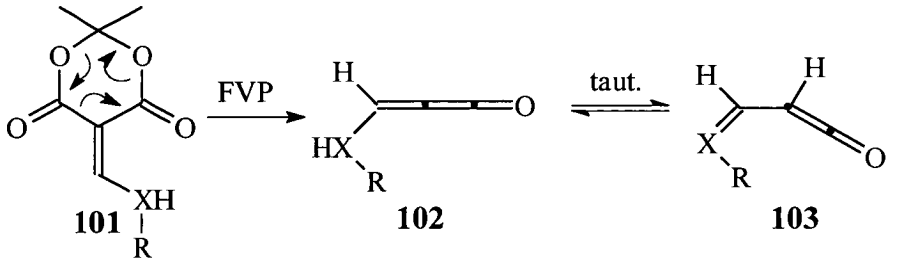


Scheme 35

Compound **94** forms the bicyclic aziridine **97** which undergoes C-C bond cleavage to form azomethine ylide intermediate **98**. Isomerisation gives intermediate **99** and a 1,7-dipolar electrocyclisation reaction yields **95**. Electrocyclisation to the central double bond gives **100** and loss of CH_4 gives **96**.[34]

1.3.4 Apparent Nucleophilic Addition.

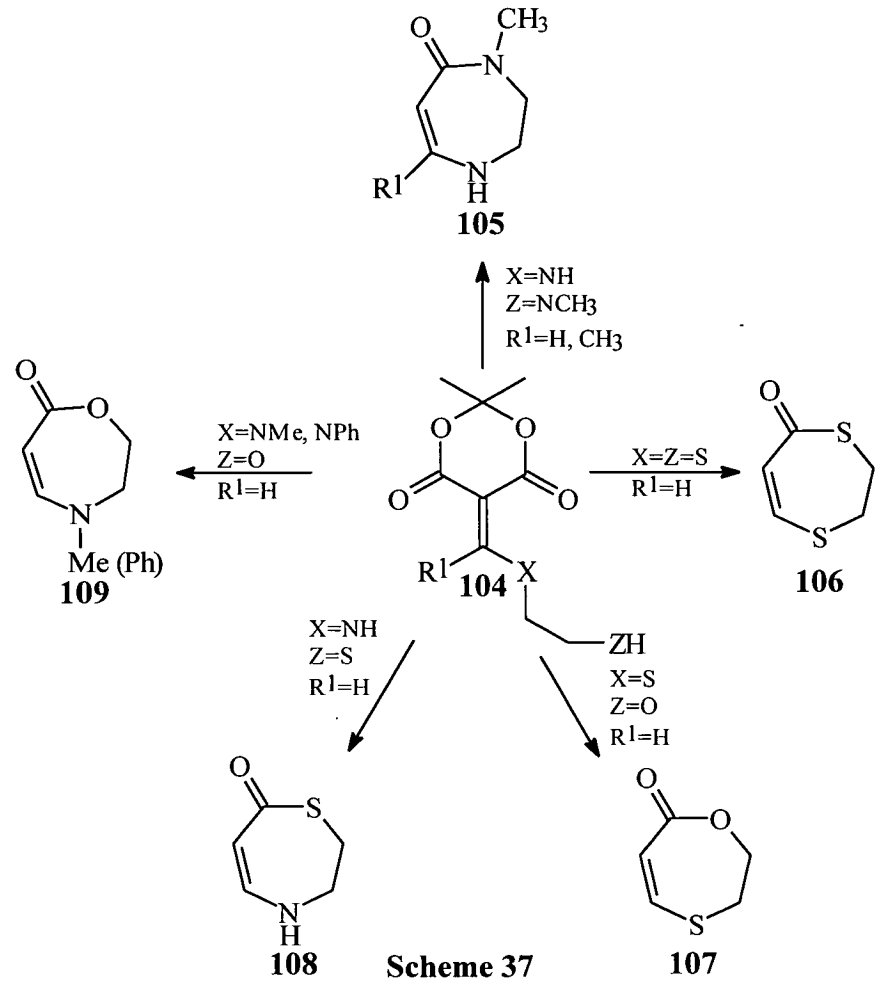
Jourdain and Pommelet[35] have reported the preparation of medium and large sized enaminolactone and thiolactone derivatives. These systems have been synthesised from Meldrum's acid derivatives using flow pyrolysis conditions at temperatures of 400 - 500 °C. The key intermediate in the pyrolysis of Meldrum's acid derivatives **101** is the formation of a methyleneketene intermediate **102**, as shown in **Scheme 36**. The methyleneketene intermediate is a tautomer of the iminoketene **103**.



101 **102** **103**

Scheme 36

A variety of Meldrum's acid derivatives were subjected to flow pyrolysis conditions and resulted in the formation of seven membered heterocycles in moderate to good yield and are illustrated in **Scheme 37**. These Meldrum's acid derivatives sublime with difficulty and largely decompose in the inlet. To overcome this problem, these precursors were pyrolysed in a stream of acetone which is then dropped through an electrically heated, vertical quartz tube packed with quartz balls. The pyrolysis temperatures required for total conversion of the precursors under these conditions does not exceed 530 °C.

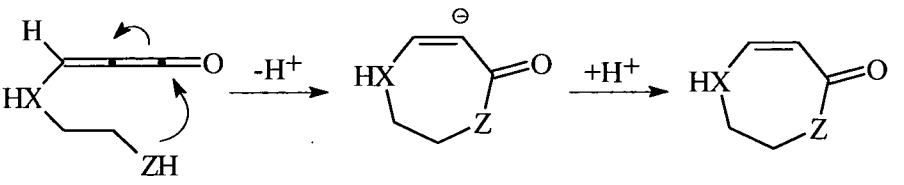


Scheme 37

The reaction is very general with diazepinones **105**, dithiepinones **106**, oxathiepinones **107**, thiazepinones **108** and oxazepinones **109** being obtained in yields of 47 - 79%.[36, 37, 38]

Compound **107** was also tentatively identified as a product from the FVP reaction of the same precursor. This was a small scale reaction and the product was not fully characterised.[39] The reaction under flow pyrolysis conditions occurs at 420 °C and a yield of 74% is obtained. Under FVP conditions, a higher temperature of 600 °C is required for this cyclisation to take place. A yield for the FVP reaction has not been quoted.

The formation of heterocycles **105** - **109** has been rationalised by addition of the nucleophilic group to the methyleneketene, as shown in **Scheme 38**.

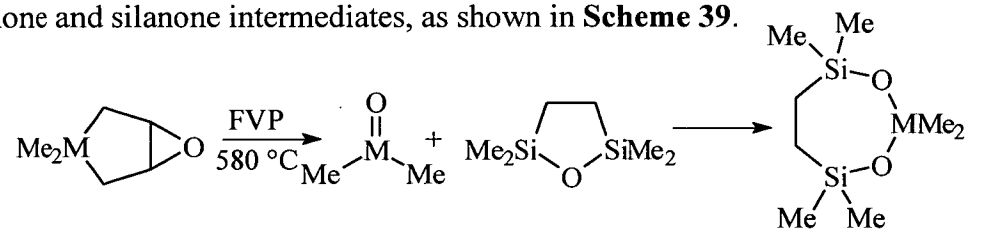


Scheme 38

However, such electrophile-nucleophile reactions are rare in the gas phase. A recent review by McNab and co-workers,[31] suggests that these reactions may occur by a concerted process involving a 4-membered transition state or that the higher pressures involved in these reactions catalyse the process in some way. The absence of a five membered ring product suggests that the cyclisations do not take place in the condensed phase on heating of the trap but must take place in the gas phase. Further work in order to clarify this mechanism would be of interest.

1.3.5 Cycloaddition Reactions.

Weber and co-workers[40, 41] have used pyrolysis reactions to identify germanone and silanone intermediates, as shown in **Scheme 39**.

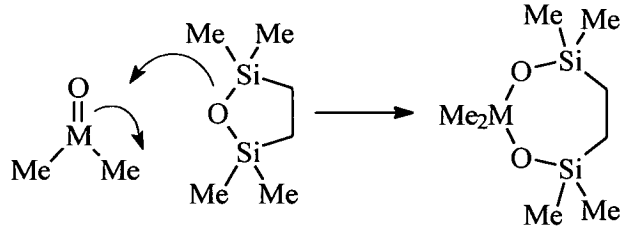


110 M=Ge; **a** Si; **b** **111** **112** **113**

Scheme 39

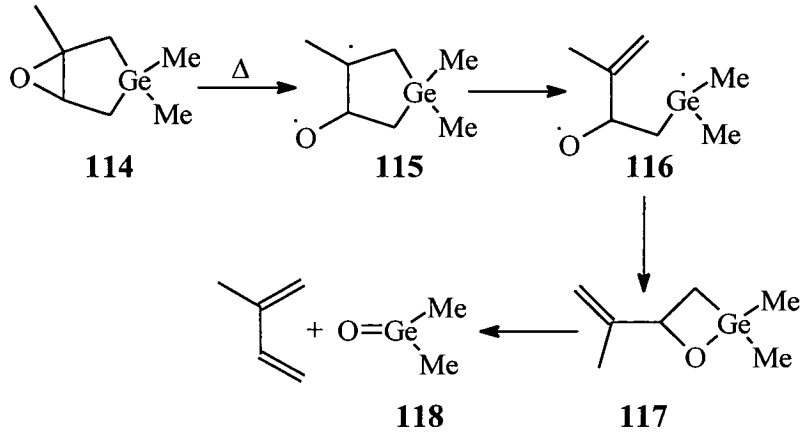
Pyrolysis of compound **110a** results in the formation of 1,1-dimethylgermanone **111a**, which has been confirmed by its insertion into compounds such as **112**, to form the seven-membered heterocycle **113a** in 40% yield.[40] In a similar reaction, compound **110b** was subjected to flash vacuum pyrolysis conditions which resulted in the formation of 1,1-dimethylsilanone **111b**, which again inserted into compound **112** to form compound **113b** in 41% yield.[41]

In these examples, the ring formation step is by a [2+2] cycloaddition mechanism, as shown in **Scheme 40**.



Scheme 40

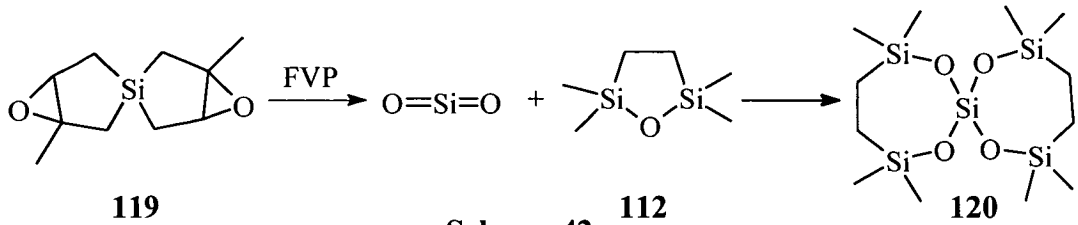
The germanone and silanone intermediates are thought to be formed by radical processes and this is shown in **Scheme 41**.



Scheme 41

When compound **114** was pyrolysed, it formed diradical **115**. This rearranged through intermediate **116** to give four-membered ring **117**. Ring opening with extrusion of 2-methyl-1,3-butadiene resulted in compound **118**.

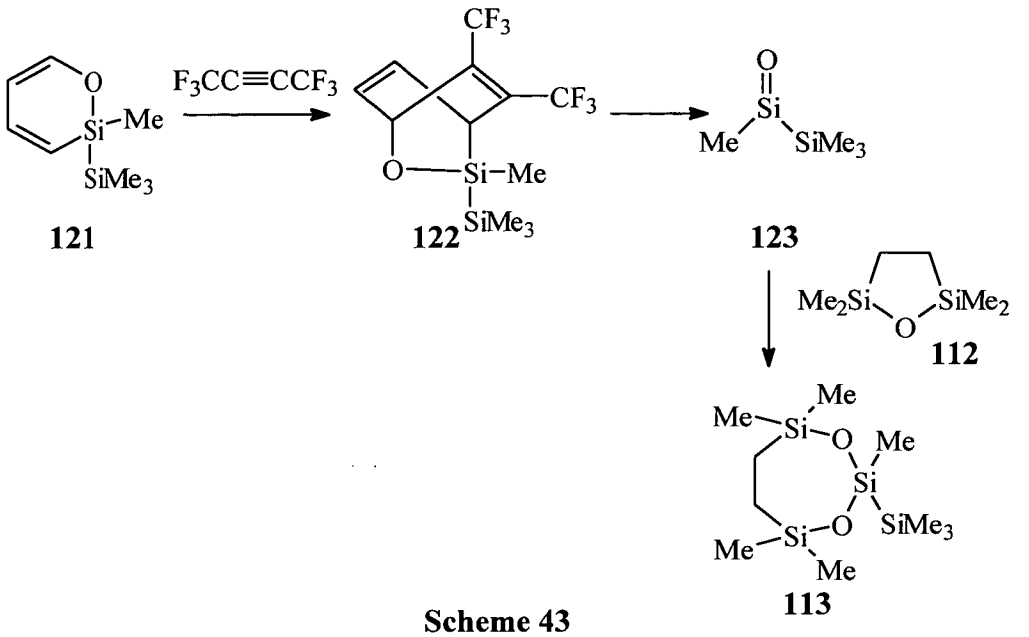
When compound **119** was subjected to FVP conditions, it resulted in the spiro compound **120** in 20% yield, as shown in **Scheme 42**. Again, this occurred *via* an insertion reaction into compound **112**.[42]



Scheme 42

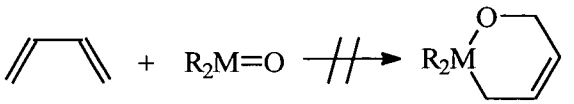
When silapyran **121** was thermolysed under flow pyrolysis conditions, in a hexafluorobut-2-yne flow in the presence of the cyclic disiloxane **112**, silanone **123**,

formed by the retro Diels-Alder reaction of the transient adduct **122**, was trapped as compound **113b**. The general reaction is shown in **Scheme 43**.[43]



Scheme 43

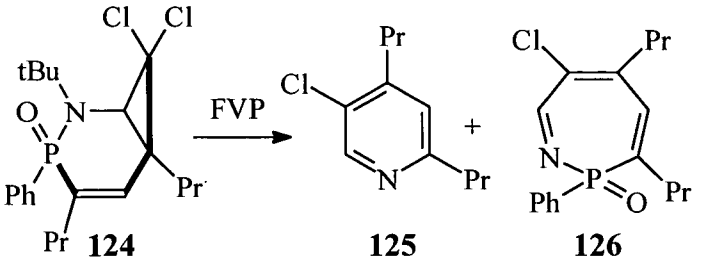
It should be noted that in all the above examples, no [4+2] cycloaddition reaction of the metallones was observed with 1,3-butadiene or isoprene even when the thermolysis were carried out in presence of an excess of diene, as shown in **Scheme 44**.



Scheme 44

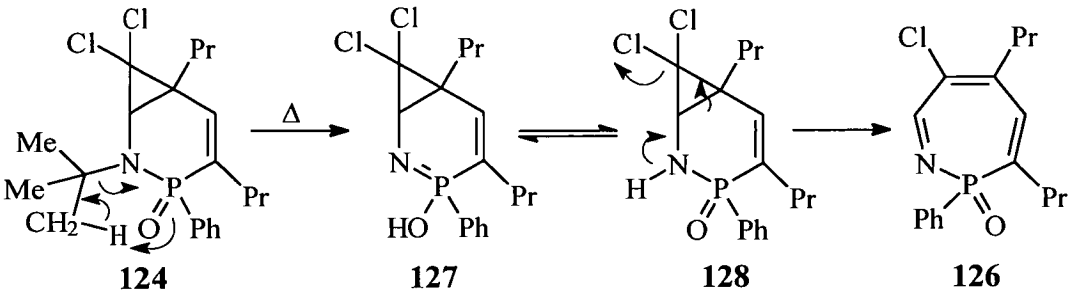
1.3.6 Retro-ene Reactions.

Foucaud and co-workers[44] subjected compound **124** to flash vacuum pyrolysis conditions at 570 °C it resulted in pyridine **125** and unstable 2*H*-1,2-azaphosphepine **126**, as shown in **Scheme 45**. However, no yields of these products have been reported.



Scheme 45

The proposed mechanism for the formation of seven-membered ring **126** is shown in **Scheme 46**.



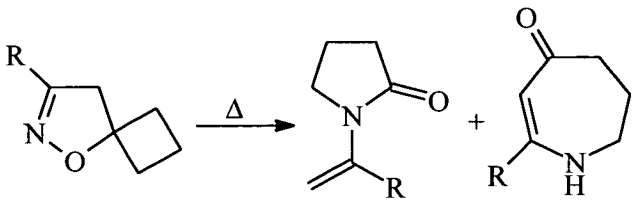
Scheme 46

Initially, compound **124** undergoes a retro-ene reaction to give compound **127**. Compound **127** can tautomerise to compound **128** which in turn undergoes a ring opening reaction with extrusion of HCl to give compound **126**. Pyridine **125** is formed by the extrusion of Ph-P=O from compound **126** and follows a mechanism similar to that shown in **Scheme 24**.

1.3.7 Radical Reactions.

Goti and co-workers[45] investigated the pyrolysis behaviour of some spirocyclobutane compounds. Under flash vacuum pyrolysis conditions, these compounds rearranged to give mainly azepin-4-one derivatives.

Compounds **129a** and **129b** were subjected to FVP conditions at 500 °C and resulted in compounds **130** and **131**, as shown in **Scheme 47**.



129 **130** **131**

a; R= Ph
b; R= Me

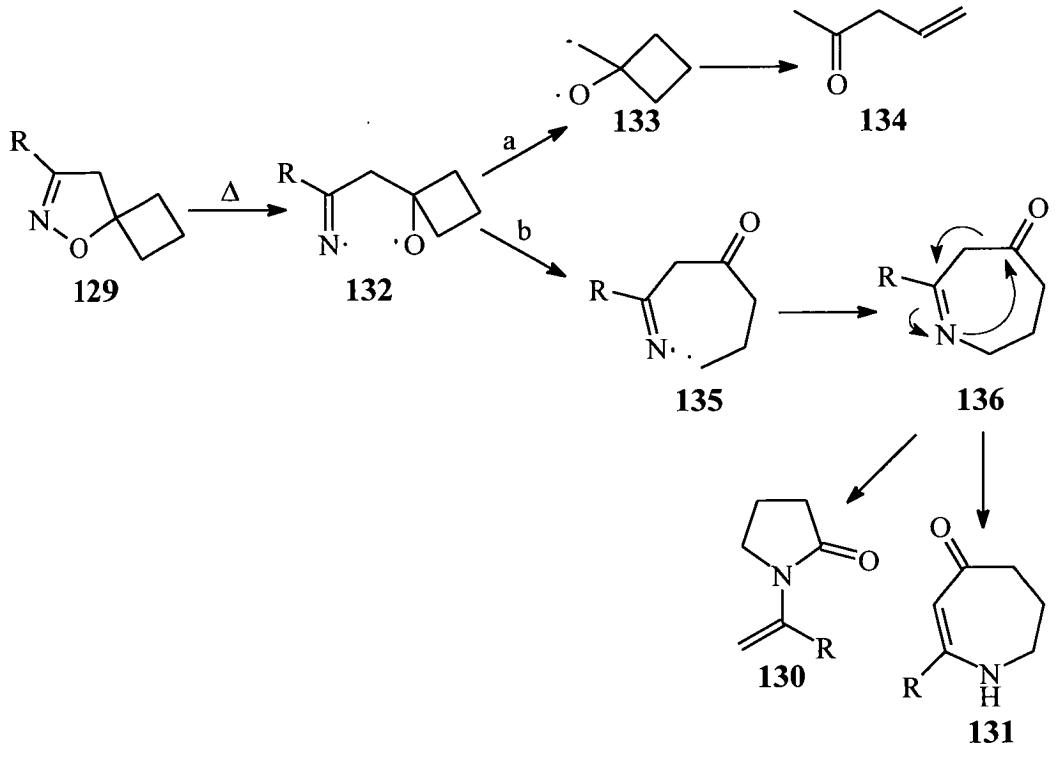
Scheme 47

Two derivatives of compound **129** were pyrolysed and the yields for each product are shown in **Table 7**. This shows that the azepinone is the major product in each case.

Precursor	Compound **130**	Compound **131**
129a	28%	37%
129b	17%	28%

Table 7- Yields of products **130** and **131** from the pyrolysis of compounds **129a** and **129b**.

The authors speculate that the above reactions occur *via* radical processes, as shown in **Scheme 48**.



Scheme 48

The stability of diradical **132** may be responsible for the observed decomposition products **134**. If there is ring opening (pathway "b") to diradical **135** then azepinone **136** will be formed which can undergo a [1,3] hydrogen shift to give compound **131** or a ring contraction to the alkenylpyrrolidinone **130.**

This methodology was used to synthesise several different derivatives and these are shown in **Table 8**.

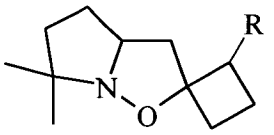
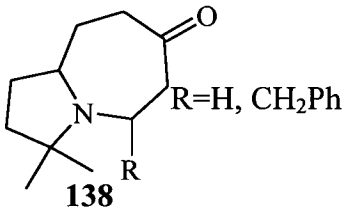
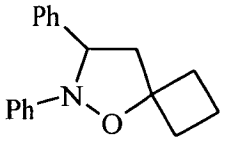
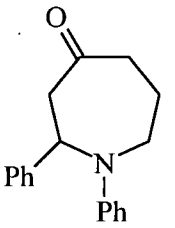
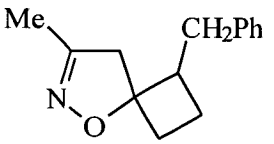
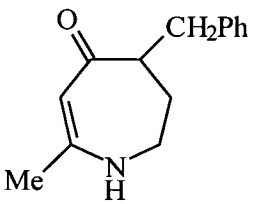
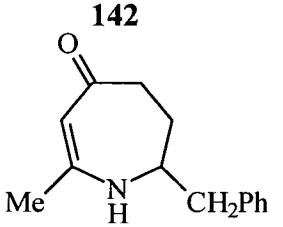
Substrate	Product	Yield
 **137** R=H, CH_2Ph	 **138**	R=H, 25% R=CH_2Ph, 3%
 **139**	 **140**	42%
 **141**	 **142**  **143**	14% 16%

Table 8: The spirocyclobutane derivatives **137**, **139** and **141** with the azepinones formed upon pyrolysis and their relative yields.

These results show that compounds **137** and **139** pyrolyse to give azepinones **138** and **140** respectively in yields of 3 - 42%. When compound **141** was subjected to FVP conditions there were two azepinones, **142** and **143**, formed with different substitution patterns in a combined yield of 30%.

The authors note that these reactions are scarcely reproducible when there is a change to the FVP conditions. A change in the vacuum of the FVP apparatus leads to decreased contact time in the hot zone for the molecules which leads to a difference in the product distribution although the overall recovery yield is not affected.

1.4 Use of Seven-membered Heterocycles As Precursors in Pyrolytic Reactions.

1.4.1 Preamble.

This section details the literature on pyrolytic reactions that use seven-membered heterocycles as precursors. The pyrolysis section falls into six sections.

These are:-

i/ Nitrene Reactions.

ii/ *Extrusions.

iii/ Retro-chelotropic Processes.

iv/ Radical Reactions.

v/ Sigmatropic Shifts.

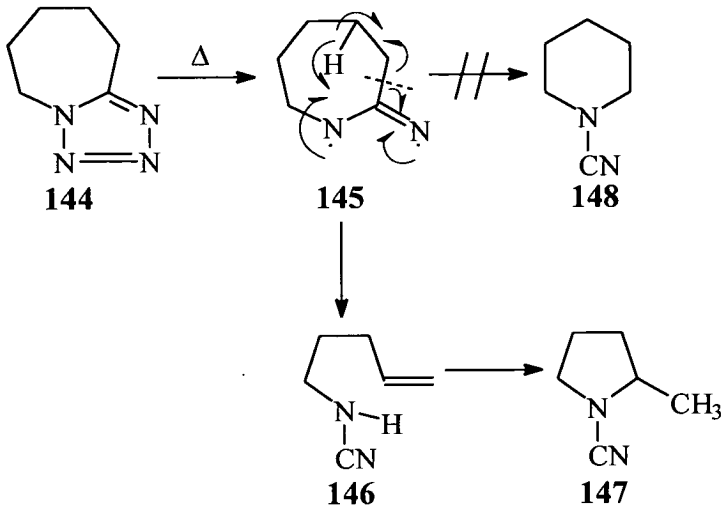
vi/ Retro-ene Reactions.

vii/ Oxidative Ring Contraction Reactions.

*In the synthesis section of this review, the description of the formation of some unstable seven-memberd heterocycles also includes its pyrolysis behaviour. In order to avoid repetition of these examples in this section, a reference back to the appropriate scheme will be made where appropriate.

1.4.2 Nitrene Reactions.

Wentrup[46] has investigated the ring fission of nitrenes derived from polymethyleneterazoles. Pyrolysis of compound **144,** at temperatures of ~550 °C produced compounds **146** and **147** in moderate yields. The general reaction is shown in **Scheme 49**.

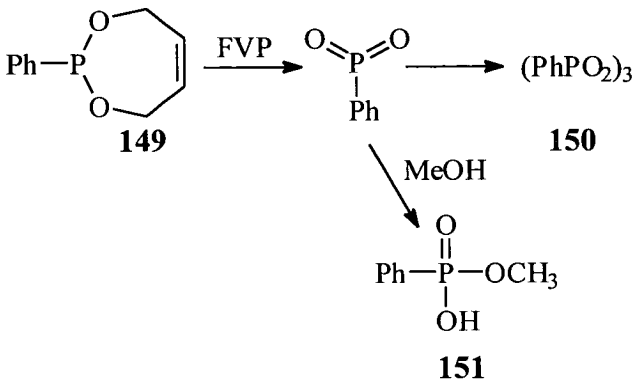


Scheme 49

Under pyrolysis conditions, compound **144** forms nitrene **145** shown in its diradical form. This undergoes radical fission and hydrogen transfer to form *N*-cyano-1-aminopent-4-ene **146** as the primary product which then cyclises to give *N*-cyano-2-methylpyrrolidine **147**. There is no evidence that the nitrene ring contracts directly to give *N*-cyanopiperidine **148**. It should be noted that the five-membered ring nitriles are important products of the gas phase ring contraction of the appropriate six-membered nitrene.

1.4.3 Extrusions.

Using flash vacuum pyrolysis, Cadogan and co-workers[47, 48] have investigated the decomposition mechanism of a series of phosphonites, an example of which is shown in **Scheme 50**.



Scheme 50

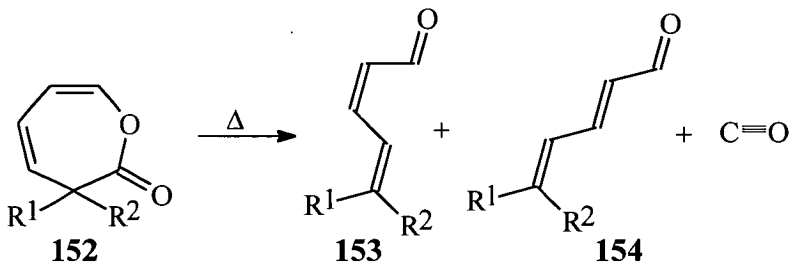
The pyrolysis of 4,7-dihydro-2-phenyl-1,3,2-dioxaphosphepine **149** is thought to produce a monomeric phosphonobenzene intermediate by the thermal elimination of

1,3-butadiene. This monomer can be trapped with methanol to give the monomethyl ester of phenylphosphonic acid **151** or it can give the trimeric metaphosphonate **150**.

Other extrusion reactions of seven-membered heterocycles are shown in **Schemes 8**, **24** and **46**.

1.4.4 Retro-Cheletropic Processes.

Skorianetz and Ohloff[49] have investigated the gas phase pyrolysis of 2(3*H*)-oxepines **152**. Two derivatives, **152a** and **152b** were pyrolysed and in each case, a solution of the precursor in toluene was dropped through a vertical tube filled with Raschig rings, at 15 Torr. The general reaction is shown in **Scheme 51**.



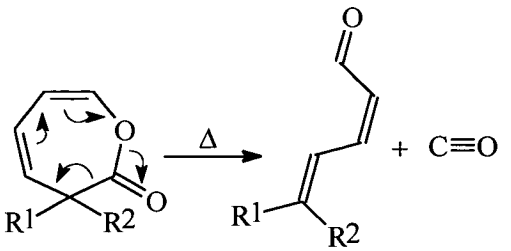
152 **153** **154**

a; R^1=Ph, R^2=Me
b; R^1=R^2=Me

Scheme 51

The pyrolysis of compound **152a** at 400 °C results in the two geometric isomers of compound **153**. The pyrolysis of dimethyl precusor **152b**, was affected by the temperature of the pyrolysis. At 400 °C, a mixture of *cis* and *trans* [This stereochemistry is about the central double bond] aldehydes (**153** and **154**) was obtained in a 3:4 ratio but at the higher temperature of 500 °C only the *trans* aldehyde **154** was obtained.

The authors suggest that compounds **152a** and **152b** undergo a retro-cheletropic process as the two bonds to the carbonyl carbon are being broken simultaneously. As a consequence of this, carbon monoxide is extruded, as illustrated in **Scheme 52**.

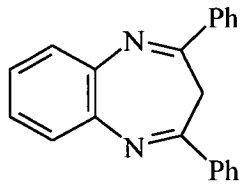


Scheme 52

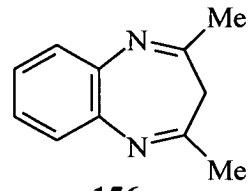
The cheletropic process results in compound **153** which has *cis* stereochemistry at the central double bond. Compound **154** which has *trans* stereochemistry at this bond is thought to be a pyrolysis product of compound **153**. There is a literature precedent for this isomerisation, where McNab and co-workers[50] found that *cis/trans* isomerisation takes place at temperatures of 650 °C and above under FVP conditions. The results of the pyrolysis of compound **152b** suggest that a temperature of 500 °C is adequate for this isomerisation to take place, under these flow pyrolysis conditions. The lower temperature for the isomerisation of **153** may be attributed to the longer contact times associated with the flow pyrolysis reaction.

1.4.5 Ring Cleavage With Formation Of Diradical Reactions.

McNab and co-workers[51] have studied the behaviour of 2,4-diphenyl- and 2,4-dimethyl-1,5-benzodiazepines (**155** and **156** respectively) under flash vacuum pyrolysis conditions. These compounds were pyrolysed at temperatures of 800 – 850 °C.

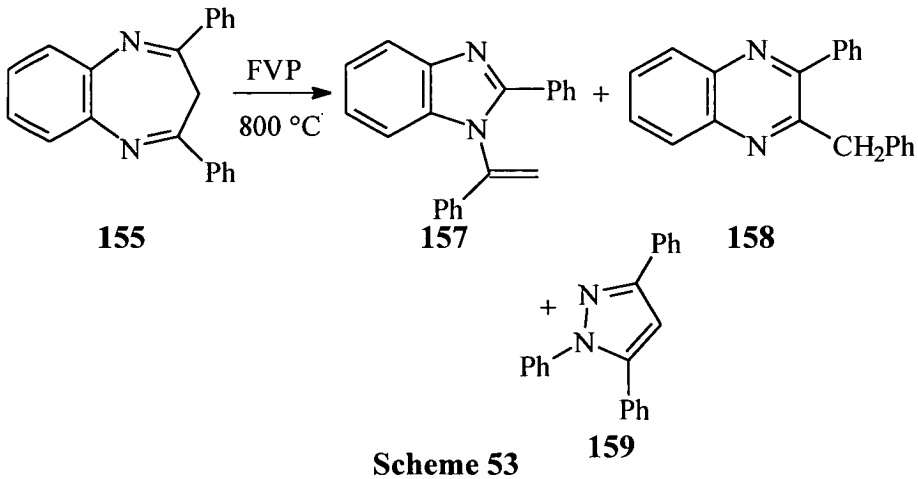


155



156

The pyrolyses of both these compounds showed that there is no clear decomposition route open to these systems as a number of different products were isolated in 1 - 15% yields from highly complex pyrolysates. The pyrolysis of compound **155** gave three products which were all isomeric with it, as shown in **Scheme 53**.

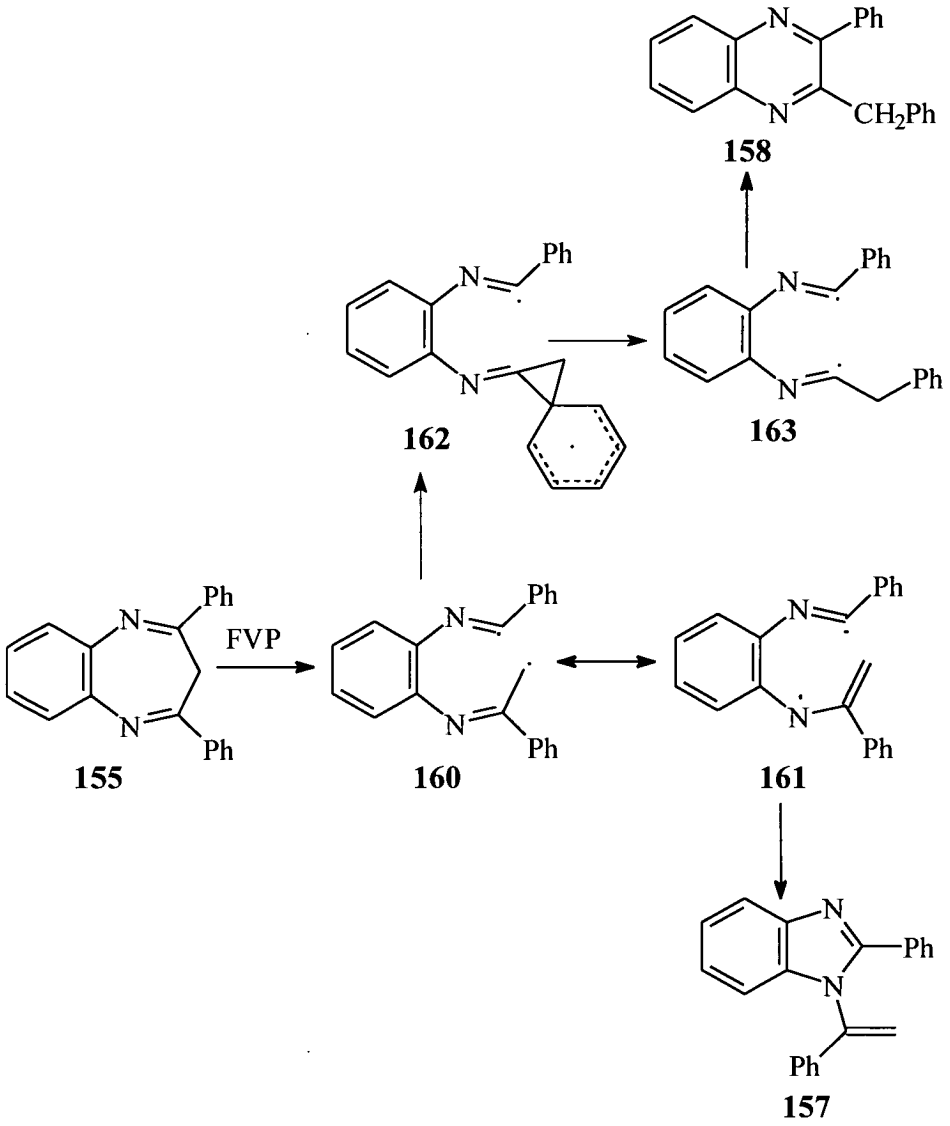


155 **157** **158** **159**

Scheme 53

The structure of compound **157** was confirmed by a series of nOe and COSY NMR experiments whereas structures **158** and **159** were confirmed by comparison with literature data.

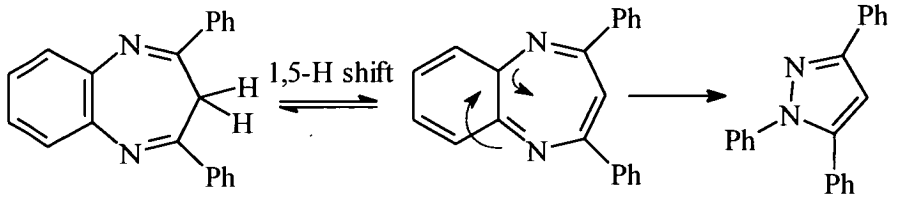
The thermal behaviour of the benzodiazepine system is therefore controlled by ring contraction reactions. A proposed mechanism for the formation of these products is given in **Scheme 54**.



Scheme 54

The initial step in the formation of **157** and **158** is the direct homolysis of the C(2) - C(3) bond of the diazepine to give the imidoyl-aza-allyl diradical pair **160/161**. Collapse of diradical **161** will result in 1-alkenylbenzimidazole **157** which is the

major product formed, though only in 12% yield. The formation of the quinoxaline **158** can be explained by a 1,2-phenyl shift in the aza-allyl unit which may be *via* a neophyl-type rearrangement. The pyrazole **159** is thought to be formed by the mechanism shown in **Scheme 55**.

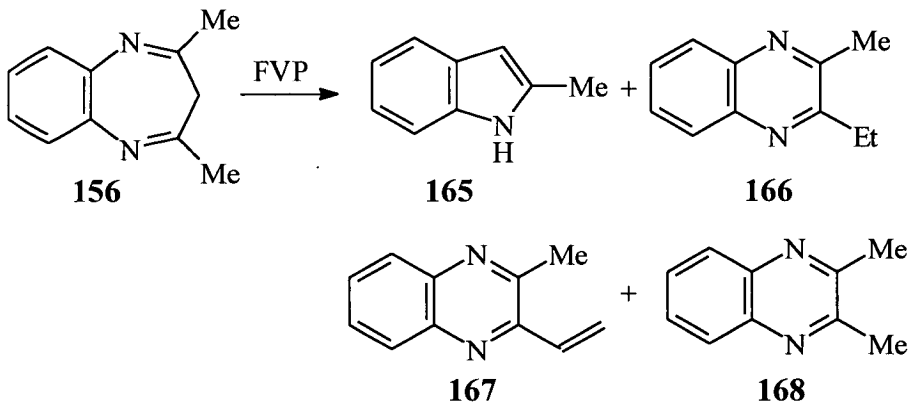


155 **164** **159**

Scheme 55

The initial step is thought to be a 1,5-hydrogen shift from the 3-position of the benzodiazepine to one of its bridgehead positions to give intermediate **164**. This is followed by simultaneous C-N bond cleavage and N-N bond formation. Rearomatisation, driven by the formation of two stabilised 6π-electron systems, yields the pyrazole **159**.

The 2,4-dimethyl-1,5-benzodiazepine **156** results in four products when subjected to flash vacuum pyrolysis condition, as shown in **Scheme 56.**



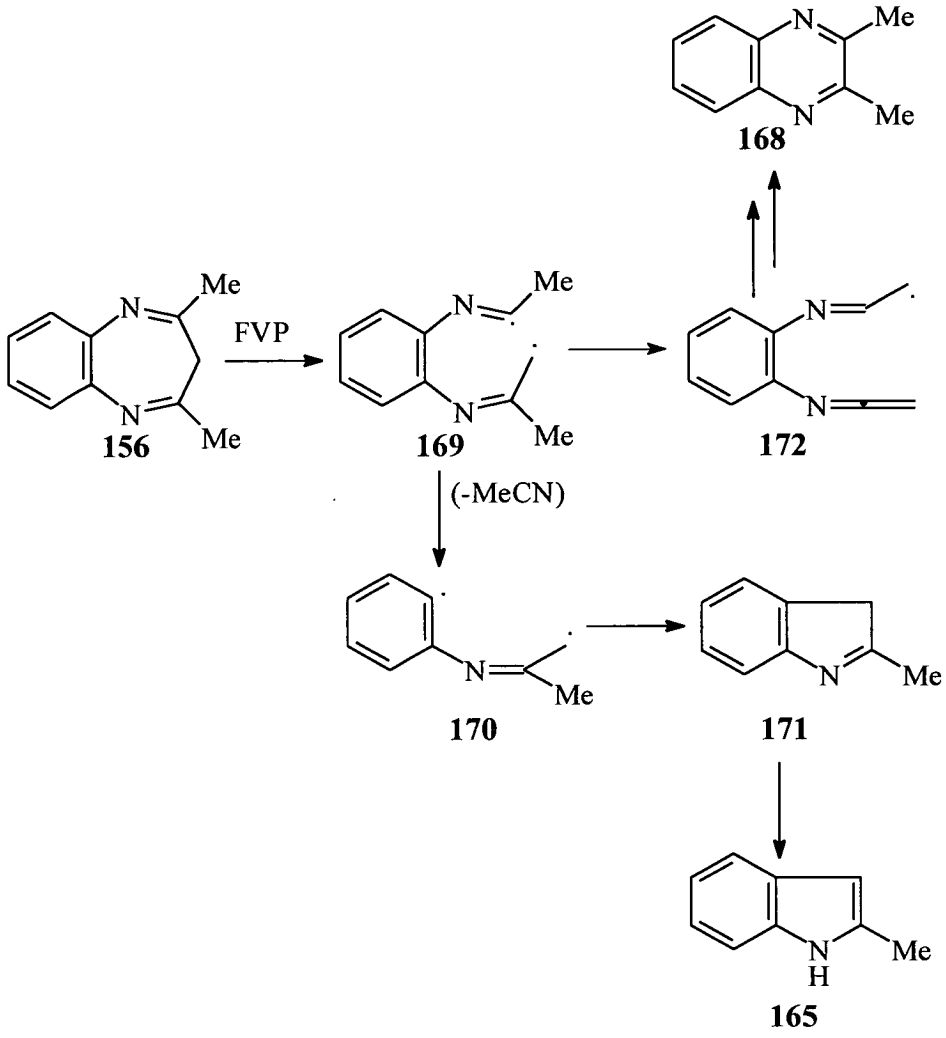
156 **165** **166**

167 **168**

Scheme 56

The structures of indole **165** and quinoxalines **166** and **168** were identified by comparison with literature spectra. However the vinylquinoxaline **167** was tentatively identified due to the similarity of its proton spectrum to that of compound **166** except for the absence of the ethyl group signals and the presence of the alkene signals.

The formation of some of these products can be rationalised, as shown in **Scheme 57**.

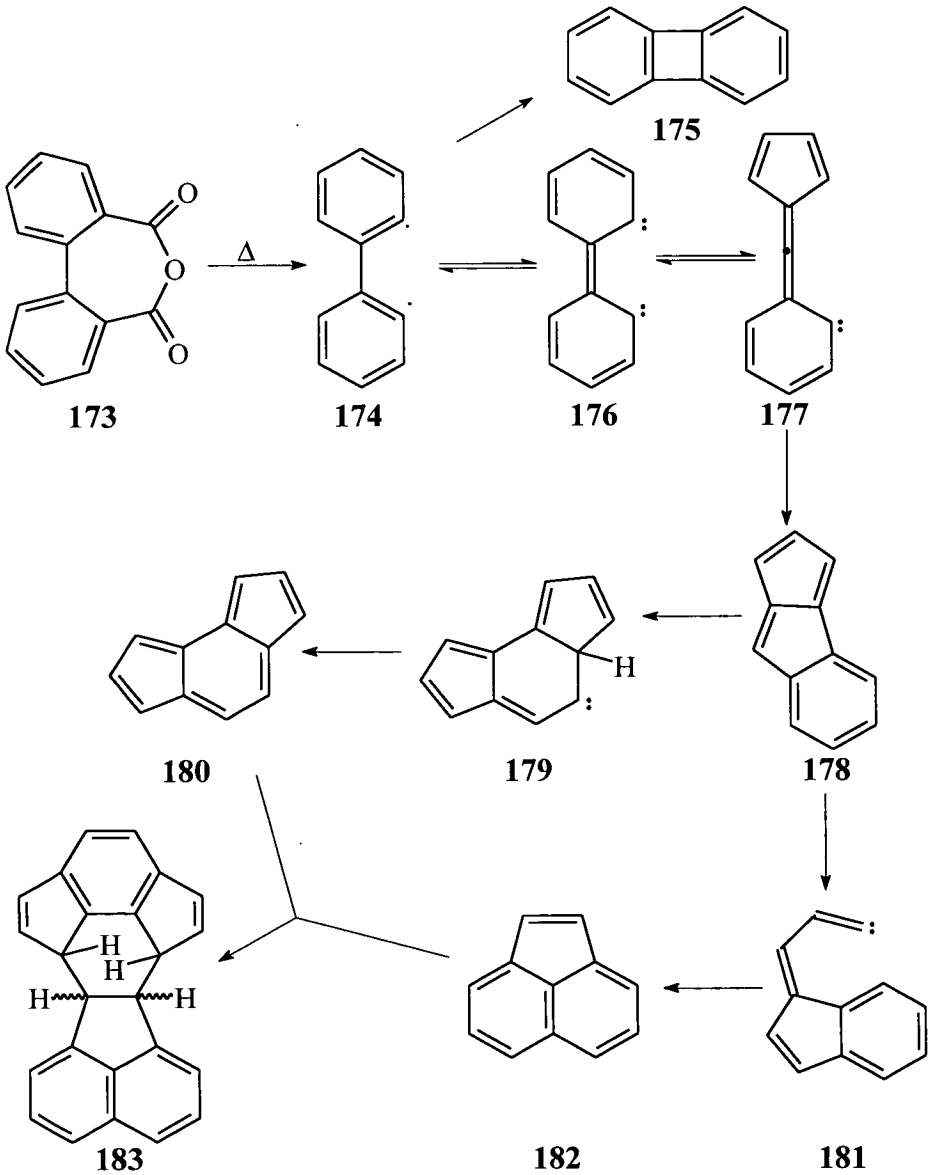


Scheme 57

Again, the initial step is to the diradical **169**, which can undergo β-cleavage to give acetonitrile and the phenyl-aza-allyl radical **170** which can collapse to give the indole **165** *via* intermediate **171**. The dimethyl quinoxaline **168** is formed by the loss of a C1 unit and one possible method is by β-cleavage. However, for the formation of the 2-methyl-3-ethylquinoxaline, the initial intermediate must undergo a 1,2-shift of a methyl group and these alkyl migrations are rare occurrences under gas phase conditions. Thermal dehydrogenation of this compound would yield the vinyl compound **167**.

Wiersum and Jenneskens[52] subjected diphenic anhydride **173** to flash vacuum pyrolysis conditions at temperatures of 850 - 900 °C. This resulted in three products, biphenylene **175**, acenaphthylene **182** and the *exo*:*endo* isomers of compound **183**, as shown in **Scheme 58**.

They tentatively proposed that the diradical **174** can be considered to exist in the bicarbenoid form **176** which undergoes a Wolff-type ring contraction to give intermediate **177**.[53] Carbene insertion and hydrogen migration forms the cyclopent[*a*]indene **178** from **177**. The *as*-indacene **180** can be rationalised from **178** by a ring contraction-ring expansion mechanism to carbene **179** followed by a 1,2-hydrogen shift. It is suggested that **178** can also undergo homolytic bond cleavage of a carbon-carbon bond of the annulated cyclopentadiene ring and a sequential 1,5-hydrogen shift to the carbenoid species **181** which forms **182** after a C-H insertion.[54] It is then thought that **180** acts as a highly reactive diene in the Diels-Alder reaction with dienophile **182** to give two isomers of **183**.



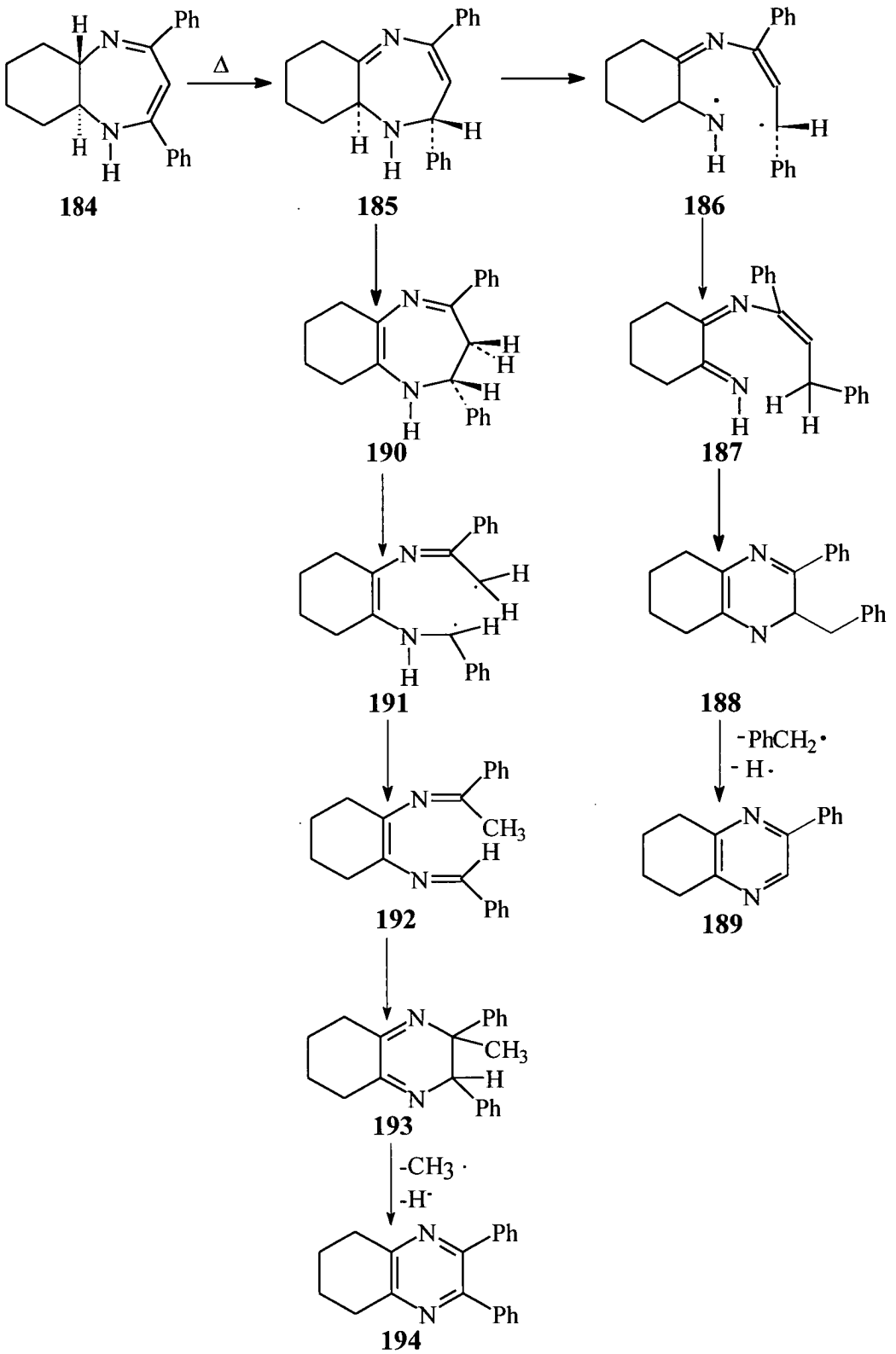
173 **174** **175** **176** **177** **178** **179** **180** **181** **182** **183**

Scheme 58

At high temperatures (750 °C), the pyrolysis reactions of 2,3-dihydro-1,4-diazepines are dominated by radical processes. [The lower temperature pyrolytic behaviour of these systems is discussed in **Section 1.4.6**.].[55] Compound **184** was pyrolysed and resulted in two products, 2-phenyl-5,6,7,8-tetrahydroquinoxaline **189** in 46% yield and 2,3-diphenyl-5,6,7,8-tetrahydroquinoxaline **194** in 4% yield. The proposed mechanism for the formation of these products is shown in **Scheme 59**.

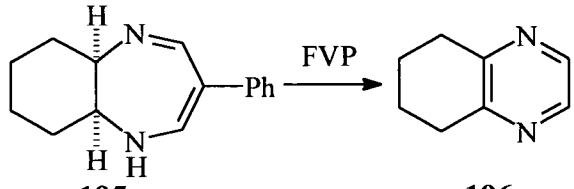
Initially, there is a 1,5-hydrogen shift to give 2,7-dihydrodiazepine **185** which undergoes a C-N bond cleavage to give diradical **186**. This diradical is stabilised by both a terminal phenyl group and a pentadienyl moiety. This undergoes consolidation to produce intermediate **187** which is followed by an electrocyclisation reaction to give intermediate **188**. Cleavage of a benzyl radical affords the major product **189**.

The minor product can be rationalised in a similar manner; from **185** a further 1,5-hydrogen shift occurs to give **190** which undergoes a C-C bond cleavage to give diradical **191**. Consolidation followed by an electrocyclisation reaction gives **192** and loss of a hydrogen and a methyl radical gives the product **194**.



Scheme 59

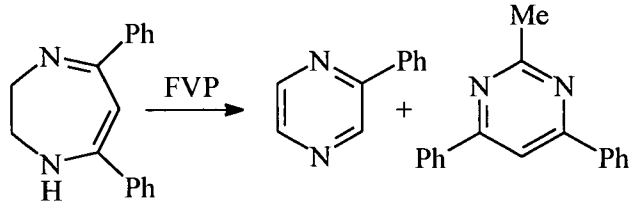
The 6-phenyl compound **195** gives compound **196** as the major product after pyrolysis, as shown in **Scheme 60**. The mechanism is thought to be similar to that for compound **194** formation with the phenyl-stabilised pentadienyl again the key intermediate.



195 **196**

Scheme 60

In the same communication, McNab and co-workers briefly mention the flash vacuum pyrolysis behaviour of 2,3-unsubstituted analogues where more complex mixtures of products were obtained, such as is illustrated in **Scheme 61**. Compound **197** results in 2-phenylpyrazine **198** in 21% yield and 2-methyl-4,5-diphenylpyrimidine **199** in 19% yield.

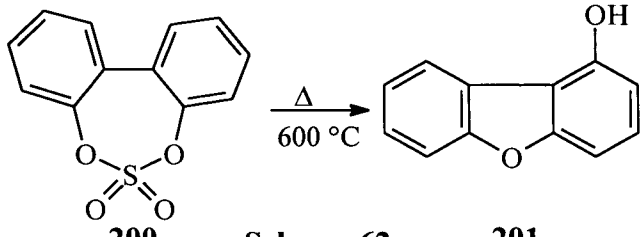


197 **198** **199**

Scheme 61

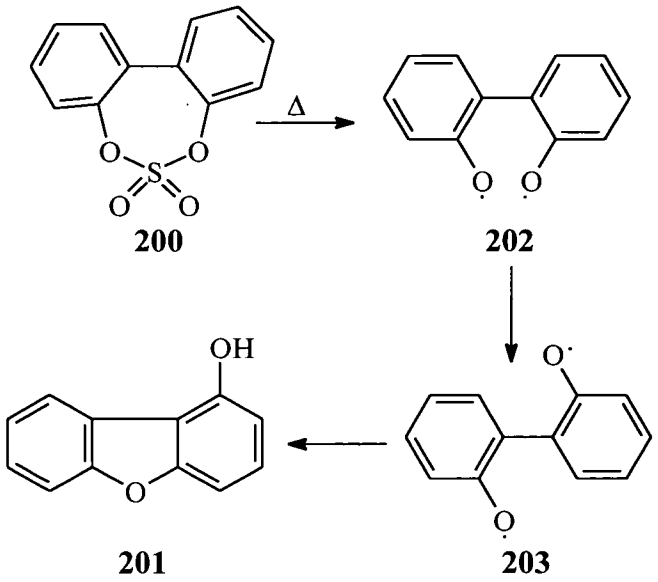
DeJongh and coworkers[56, 57] have investigated the pyrolysis reactions of cyclic aromatic sulfites and carbonates. In each case, the substrate was pyrolysed over a nichrome wire at 600 °C in a stream of nitrogen at a system pressure of 5mmHg.

The pyrolysis of compound **200** resulted in the formation of 1-hydroxydibenzofuran **201** in a yield of 89%, as shown in **Scheme 62**.



200 **Scheme 62** **201**

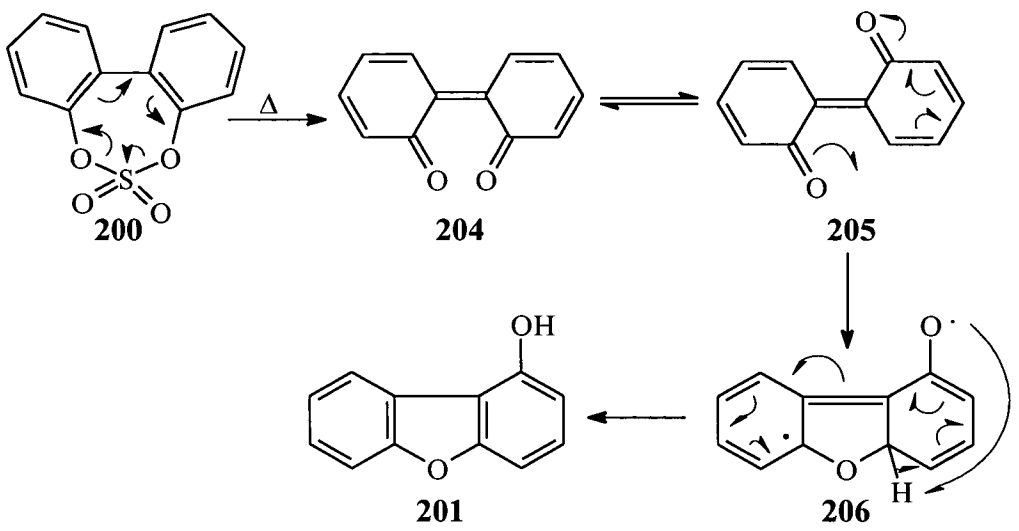
This was formed by the extrusion of sulfur dioxide from precursor **200**. In this early work, the authors did not consider the reaction mechanism in detail. There are two possible mechanisms; a diradical mechanism shown in **Scheme 63** and a cheletropic process shown in **Scheme 64**.



200 **202** **201** **203**

Scheme 63

The extrusion of sulfur dioxide forms the diradical **202**. Rotation about the ring-linking bond gives the diradical **203** which cyclises to give 1-hydroxydibenzofuran **201**.

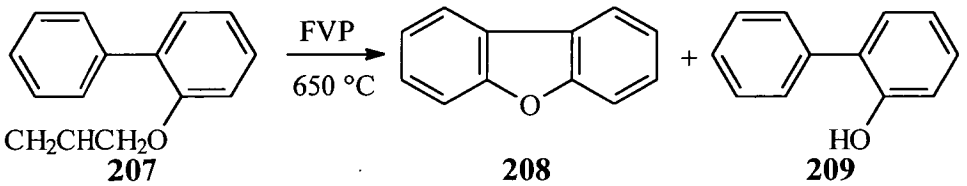


200 **204** **205** **201** **206**

Scheme 64

Here the cheletropic extrusion of sulfur dioxide results in intermediate **204** and its geometric isomer **205**. Compound **205** can cyclise by a radical mechanism to give 1-hydroxydibenzofuran **201** *via* intermediate **206**.

Work by McNab and co-workers[58] found that the FVP of 2-alloxybiphenyl **207** results in compound **208** in 65% yield and compound **209** in 17% yield, as shown in **Scheme 65**.

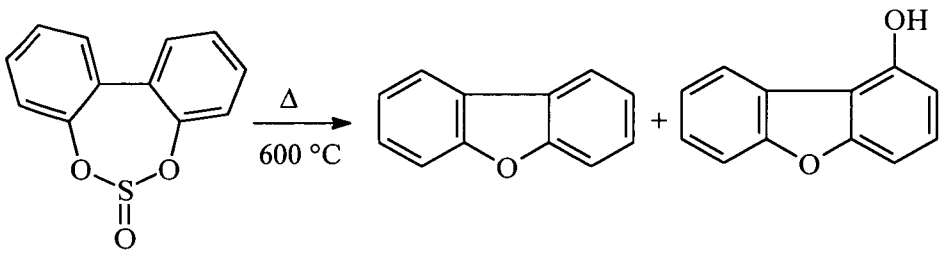


207 **208** **209**

Scheme 65

Formation of dibenzofuran suggests that of the two proposed mechanisms, the radical mechanism, shown in **Scheme 63** is the more plausible pathway for this reaction.

Compound **210** was pyrolysed under similar conditions, and in this case two products were formed, 1-hydroxydibenzofuran **201** in 52% yield and dibenzofuran **208** in 22% yield, as shown in **Scheme 66**.

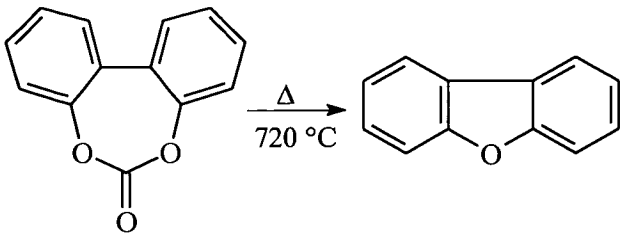


210 **208** **201**

Scheme 66

Dibenzofuran **208** results from extrusion of sulfur dioxide from **210** whilst 1-hydroxydibenzofuran **201** requires the extrusion of sulfur monoxide. It should also be noted that the dibenzofurans were recovered in high yields when they themselves were pyrolysed under identical conditions.

When the corresponding carbonate **211** was pyrolysed using the same apparatus, only decarboxylation product **208**, was isolated, in 80% yield, with no product corresponding to the extrusion of carbon monoxide and is illustrated in **Scheme 67**.

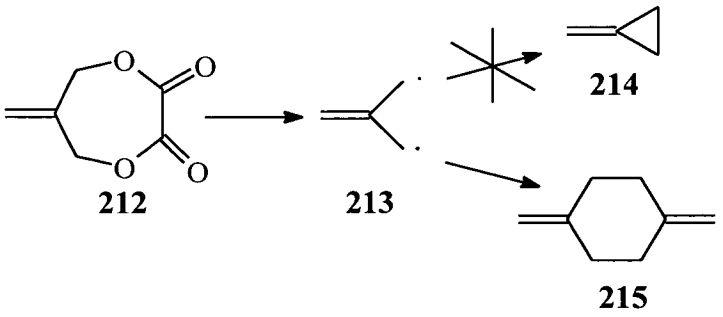


211 **208**

Scheme 67

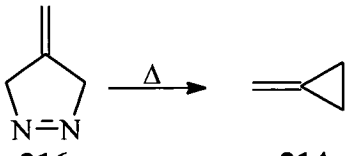
It should also be noted that a substantially higher pyrolysis temperature is required.

Schirmann and Weiss[59] investigated the pyrolysis of the cyclic oxalate **212** by introducing it dropwise, in a nitrogen stream, to a steel tube held at 450 °C. It is proposed that trimethylenemethane **213** is generated which dimerises to give 1,4-dimethylenecyclohexane **215** in low yield. There is no evidence to suggest that the other possible cyclisation product methylenecyclopropane **214** was formed, as illustrated in **Scheme 68**.



Scheme 68

The authors suggest that diradical **213** exists as the ground state triplet and therefore does not cyclise to the methylenecyclopropane **214**. Cameron and Crawford[60] have, however, shown that the methylenecyclopropane is the sole product on pyrolysis of 4-methylene-1-pyrazoline **216** at 188 °C, as shown in **Scheme 69**. The exact conditions of this pyrolysis have not been reported.



216 **214**

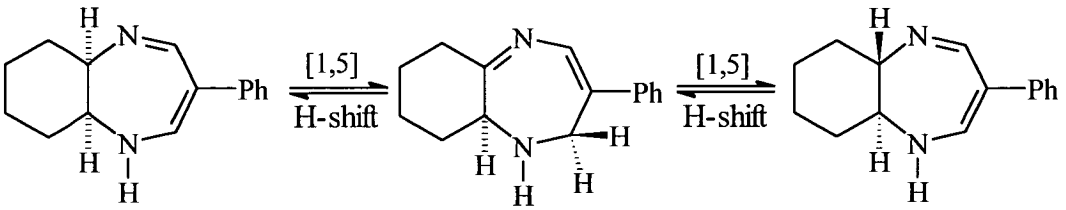
Scheme 69

However, this product may not be stable at the higher temperatures used by Schirmann and Weiss.

1.4.6 Sigmatropic Shifts.

McNab and co-workers[55] have investigated the gas phase thermal reactions of 2,3-dihydro-1,4-diazepines. Such reactions have been found to involve the saturated portion of the molecules and to be controlled by hydrogen shift reactions from the 3-position.

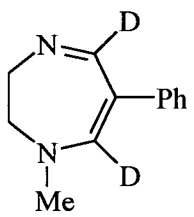
Initially, the *cis*-cyclohexane derivative **217** was pyrolysed at temperatures of 450 - 550 °C and the known *trans* isomer **218** was identified as the major product in the pyrolysate at higher temperatures. This novel *cis/trans* isomerisation was rationalised in terms of sequential 1,5-hydrogen shifts between the 3- and 7-positions, as shown in **Scheme 70**.



217 **218**

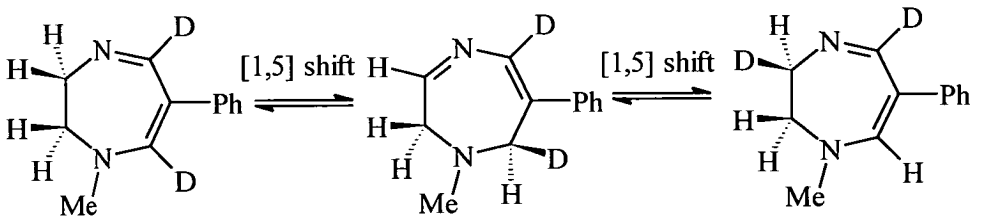
Scheme 70

The authors have studied these shifts in detail using deuterium labelling experiments, with deuteriated compound **219**.



219

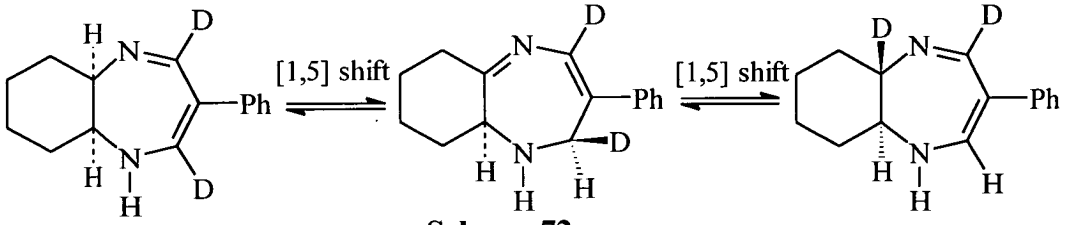
It was necessary to employ an *N*-substituted diazepine otherwise rapid prototropic shifts involving the 1H moiety would render the 1- and 4-, 5- and 7-, and 2- and 3-positions equivalent and hence no useful information could be extracted from deuterium NMR spectra. Spectral analysis of the pyrolysate of compound **219** showed label incorporation at position 3 (and not position 2) concominant with the loss of the label at position 7 (and not position 5). These findings are in agreement with the specific occurrence of 1,5-hydrogen shifts in the lowest thermal pathway available to the ring system, as shown in **Scheme 71**.



219

Scheme 71

A further labelling experiment was used to establish the suprafacial nature of the sigmatropic shift as shown in **Scheme 72**.



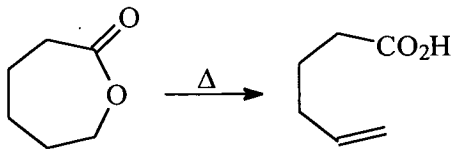
Scheme 72

If protium transfer across the top of the π surface is followed by deuterium transfer across the bottom of the surface, the amount of deuterium incorporation at the 3-position should match exactly with the measured *cis/trans* ratio. At 450 °C, the deuterium incorporation at the 3-position was 5.0:1 and the degree of isomerisation was 5.3:1. A similar relationship was observed at 500 °C with the appropriate ratios being 1.15:1 and 1.17:1 respectively. This data confirms the aforementioned relationship.

1.4.7 Retro-ene Reactions.

The pyrolysis of lactones has been studied by Bailey and Bird.[61] In each experiment, the pyrolysis precursor had nitrogen bubbled through it for several minutes and was then dropped through a vertical pyrolysis tube packed with Vycor Raschig rings. The product was dissolved in 50% ethanol and titrated at -5 °C using standard sodium hydroxide solution.

In the first example, ξ-caprolactone **220** was used as a pyrolysis precursor and this resulted in the formation of compound **221**, as shown in **Scheme 73**.

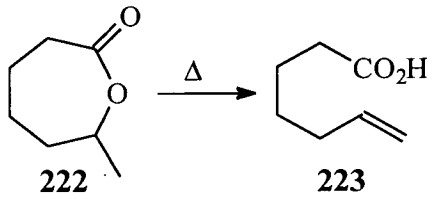


220 **221**

Scheme 73

This acid was identified initially by infrared spectroscopy which gave no evidence of a methyl group, a *cis* or *trans* double bond which indicated little or no isomerisation from the 5-hexenoic acid to the 4-hexenoic acid. The acid was then converted to its *p*-toluide and *p*-bromophenacyl ester which are both known compounds.

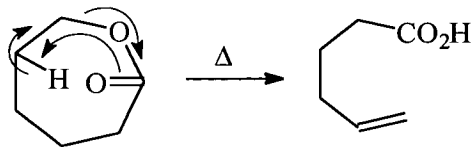
This work was extended to ξ-methyl-ξ-caprolactone **222** which was found to produce compound **223** on pyrolysis, as shown in **Scheme 74**.



222 **223**

Scheme 74

This acid was characterised as described earlier. The mechanism for these reactions is thought to occur *via* a retro ene reaction, as shown in **Scheme 75**.

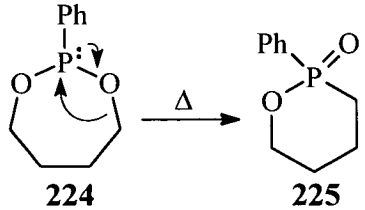


Scheme 75

A similar mechanism occurs for the methyl derivative with the elimination taking place on the methyl group.

1.4.8 Oxidative Ring Contraction Reactions.

Compound **224** results in the phostone **225** when subjected to flash vacuum pyrolysis conditions, as shown in **Scheme 76**. It should be noted however, that the conditions of the pyrolysis and the yield for this reaction have not been reported.[46, 47]



224 **225**

Scheme 76

This introduction has reviewed the available literature on the pyrolytic syntheses and reactions of seven-membered heterocycles and this theme is continued through the following discussion chapters.

The first discussion chapter discusses the formation of seven-membered heterocycles, by the radical ring expansion reactions of *N*-(4-chlorophenoxymethyl)pyridinone systems and their benzo-fused analogues.

The second discussion chapter discusses the attempted synthesis of thiepinones and azepinones and their benzo-fused analogues by the pyrolysis of the appropriate Meldrum's acid derivative.

The third discussion chapter discusses the formation of pyrrolo[3,2,1-*jk*]carbazole by the pyrolysis of 5-allyl-5*H*-dibenzo[*b*,*f*]azepine. This was formed by the cyclisation of 2-(indol-1-yl)phenyl radicals.

The fourth chapter discusses the use of the allyl ester as a phenyl radical generator in the pyrolytic synthesis of 2-(indol-1-yl)phenyl radicals.

The fifth chapter discusses the formation of these phenyl radicals using the nitro group as a radical generator.

2. DISCUSSION.

1. Flash Vacuum Pyrolysis.

The apparatus used for flash vacuum pyrolysis is illustrated in **Figure 1**.

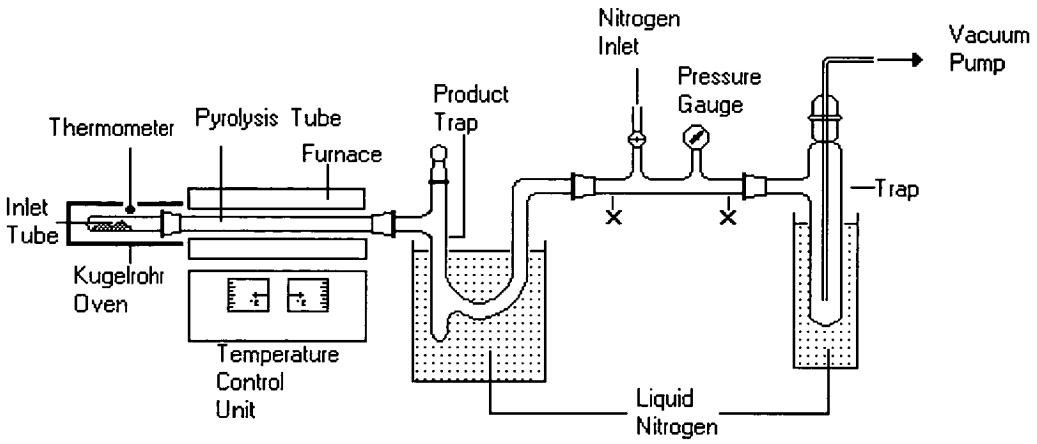


Figure 1

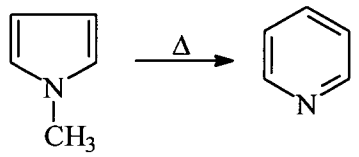
The substrate is placed in the horizontal inlet tube and is heated by a glass Kugelrohr oven, which causes it to volatilise through a silica furnace tube, held at the desired temperature by a furnace. The apparatus is maintained at a vacuum of 10^{-2}-10^{-3} Torr by a rotary oil pump. The products are collected in a U-shaped trap, cooled in liquid nitrogen and situated at the exit point of the furnace.

The apparatus ensures that the substrate is in the hot zone for a very short contact time (~milliseconds). The low concentration of molecules coupled with the short contact time results in intramolecular, rather than intermolecular reactions occurring, although there is some evidence of radical coupling reactions. Such reactions have advantages over condensed phase reactions which occur in the presence of substrates, products and solvents which can result in unwanted side reactions.

A. RADICAL RING EXPANSION REACTIONS.

2.2 Preamble.

Low yield ring expansion reactions of 5-membered heterocycles to 6-membered heterocycles have been known since 1905.[62] An example is shown in **Scheme 77** where *N*-methylpyrrole **226** results in pyridine **227**, when exposed to pyrolysis conditions.

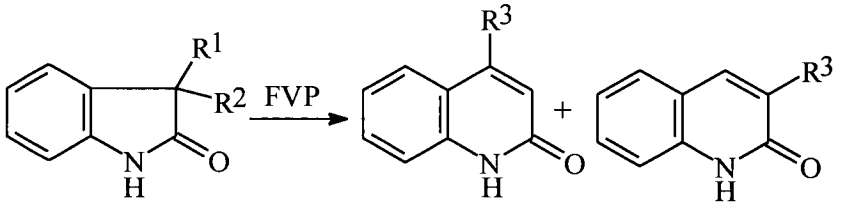


226 **227**

Scheme 77

Similar reactions are observed for the *N*-methylindole and *N*-methylcarbazole derivatives, and these result in quinoline and phenanthridine respectively.

Further work on these reactions was carried out by Patterson and co-workers[63, 64] in the 1960s but there were still no mechanistic details of these reactions reported. In 1973, Brown and Butcher[65] discovered that 3,3-dimethyloxindole **228a** undergoes an unexpected ring-expansion reaction to give quinolin-2-one **229a** under FVP conditions, as shown in **Scheme 78**.



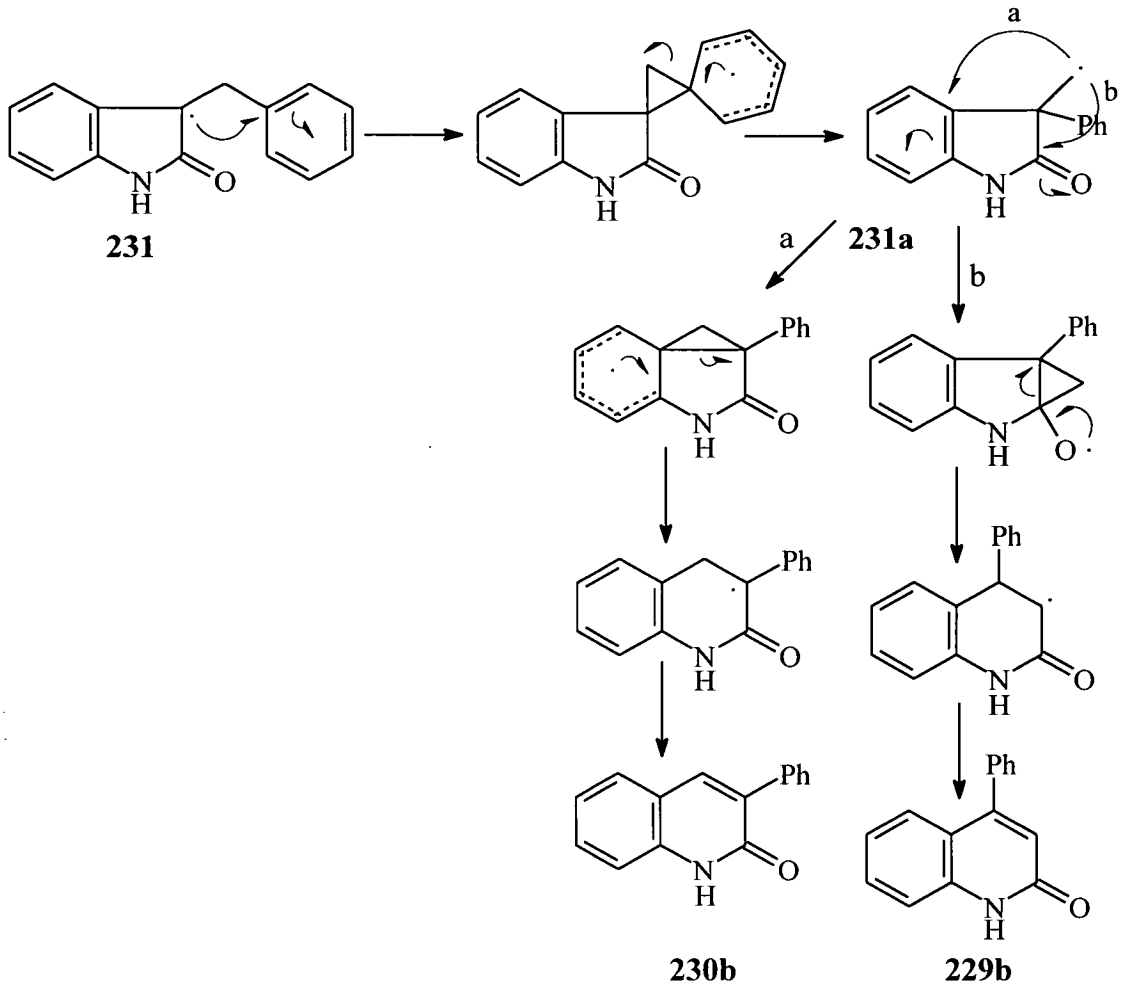
228 **229** **230**

a; $R^1=R^2=Me$
b; $R^1=R^2=CH_2Ph$

a; $R^3=H$
b; $R^3=Ph$

Scheme 78

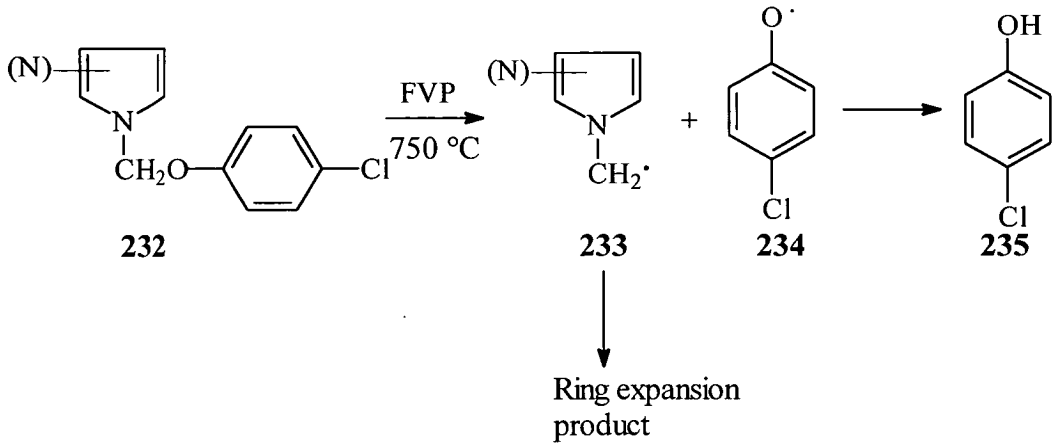
In 1990, McNab[66] reported a mechanistic study on the pyrolysis behaviour of compound **228b**. This resulted in the formation of 3- and 4-phenylquinolinones **230b**:**229b** in a 3:1 ratio. The formation of these two compounds suggests that radical **231**, which is formed on pyrolysis of compound **228b**, has two pathways open to it, as shown in **Scheme 79**.



Scheme 79

In this mechanism, a neophyl rearrangement is invoked to generate the 3-indolylmethyl radical **231a** which can lead to compound **230b** if pathway "a" is followed, or compound **229b** if pathway "b" is followed. This mechanism was confirmed by ^{13}C labelling experiments.

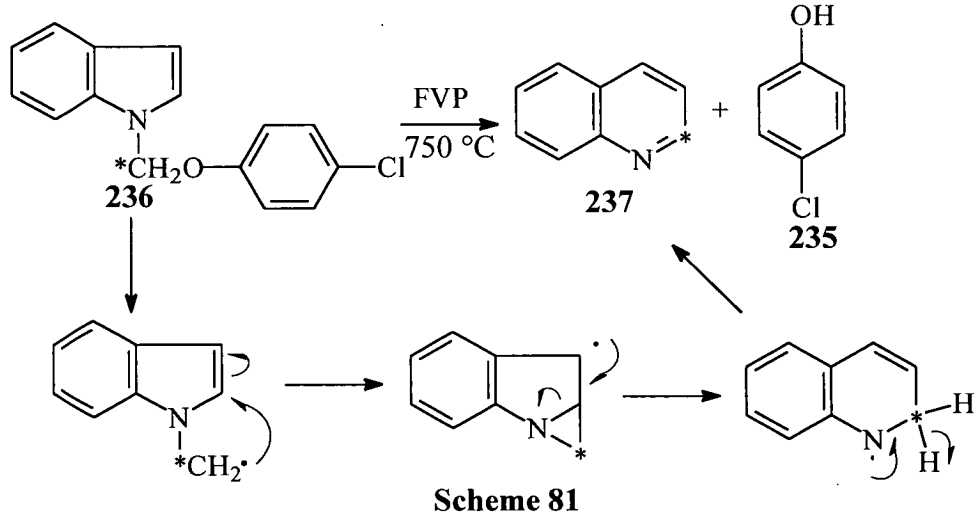
McNab and co-workers[67] then extended this work to investigate *N*-(4-chlorophenoxymethyl) substituted heterocycles, and found that they undergo ring expansion reactions under FVP conditions. Initially *N*-(4-chlorophenoxymethyl) derivatives **232** were synthesised and when pyrolysed, these were found to generate the radicals **233** and **234**. The stability of radical **234** causes the C-O bond of **232** to weaken and therefore is more likely to break under FVP conditions. Radical **234** will subsequently pick up a hydrogen atom to give *p*-chlorophenol **235** as a by-product of this reaction, as shown in **Scheme 80**.



Scheme 80

The ring expansion reactions of several different derivatives were reported including the indolyl and pyrrolyl derivatives which are described below.

The pyrolysis of the indolyl derivative **236** resulted in the formation of *p*-chlorophenol **235** and quinoline **237**. The production of quinoline and not isoquinoline as the only ring expanded product, suggested that the *N*-indolylmethyl radical **236** initiated attack exclusively at the 2-position of the indole ring. The suggested mechanism for this reaction is illustrated in **Scheme 81**. Confirmation of this mechanism was accomplished by ^{13}C labelling experiments in which the labelled methylene group appeared solely at the 2-positon of quinoline.

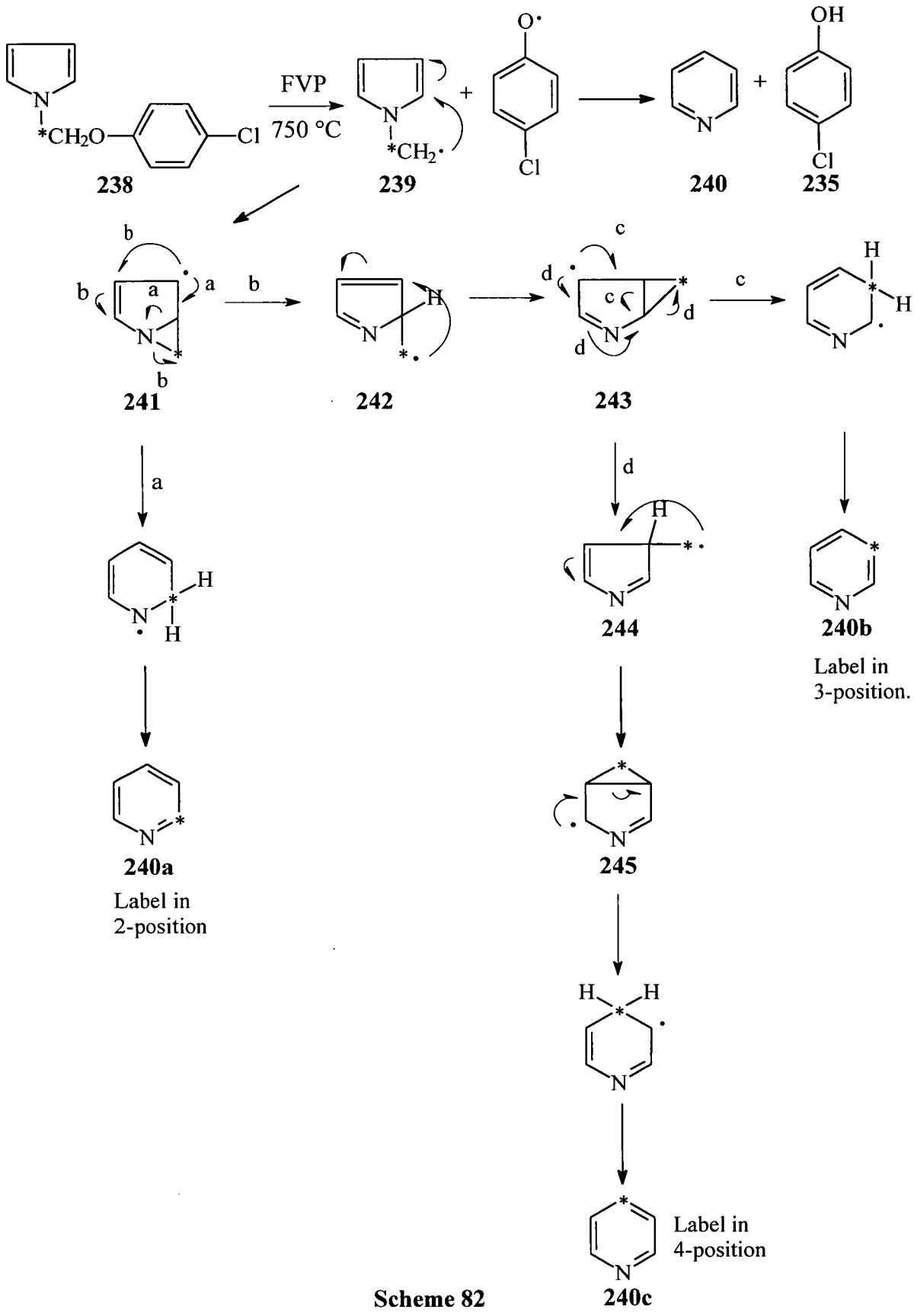


Scheme 81

When compound **238** was investigated under similar conditions, it resulted in the formation of pyridine **240** and *p*-chlorophenol **235**. When ^{13}C labelling reactions were performed on this reaction and the label occurred on all three positions of the

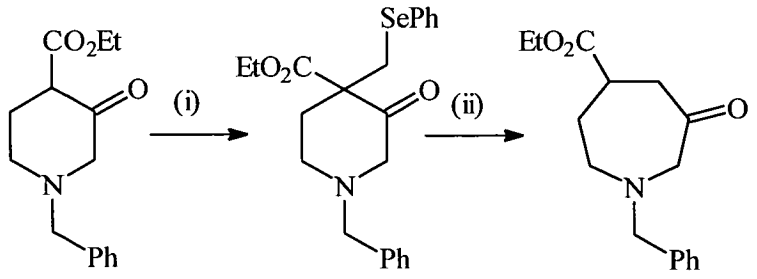
pyridine ring, it became evident that a more complex mechanism was occurring. This is shown in **Scheme 82**.

Flash vacuum pyrolysis of precursor **238** results in the *N*-pyrrolylmethyl radical **239**. This radical can insert into the double bond of the pyrrole ring to form a three membered ring **241**. This radical can then follow one of two pathways. If pathway "a" is followed, pyridine with the label in the 2-position **240a** is formed. If pathway "b" is followed, intermediate **242** is formed, which again can form a three membered ring which has walked around the ring **243**. This intermediate can again follow one of two pathways. If pathway "c" is followed, pyridine with the label in the 3-position **240b** is formed. If pathway "d" is followed, intermediate **244** is formed. This can form another three membered ring which has walked around the ring again **245**. This can result in pyridine with the label in the 4-position **240c**.


FVP
750 °C
238
239
240
235
241
242
243
244
240b
Label in
3-position.
240a
Label in
2-position
245
Label in
4-position
240c

Scheme 82

It should be noted that Dowd and co-workers[68, 69] have extensively researched ring expansion reactions in the solution phase. An example is shown in **Scheme 83**.



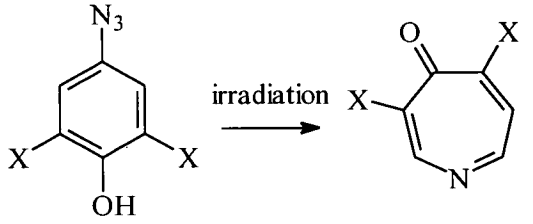
246 **247** **248**

(i) NaH, PhSeCH 2Cl, NaI
(ii) n-Bu 3SnH, AIBN

Scheme 83

Compound **246** was alkylated with chloromethyl phenyl selenide and sodium hydride in the presence of sodium iodide to give the phenylseleno adduct **247**. Tributyltin hydride reduction of **247** in refluxing benzene, with a catalytic amount of AIBN led to the ring expanded product **248** in 71% yield.

In this project, it was proposed to extend the work carried out by McNab, described in **Schemes 81** and **82**, to some six-membered systems to see if they would undergo similar ring expansion reactions. However, work by Dunkin *et al*[70], has shown that azepin-4-one systems, which would be the expected product from a ring expansion reaction of the 6-membered pyridinone systems, are unstable. In concentrated nitrogen matrices at 10 – 20 K, irradiation of compound **249** showed evidence of the azepin-4-one **250**, by infrared spectroscopy which persisted to room temperature in very low yields. This is shown in **Scheme 84**.

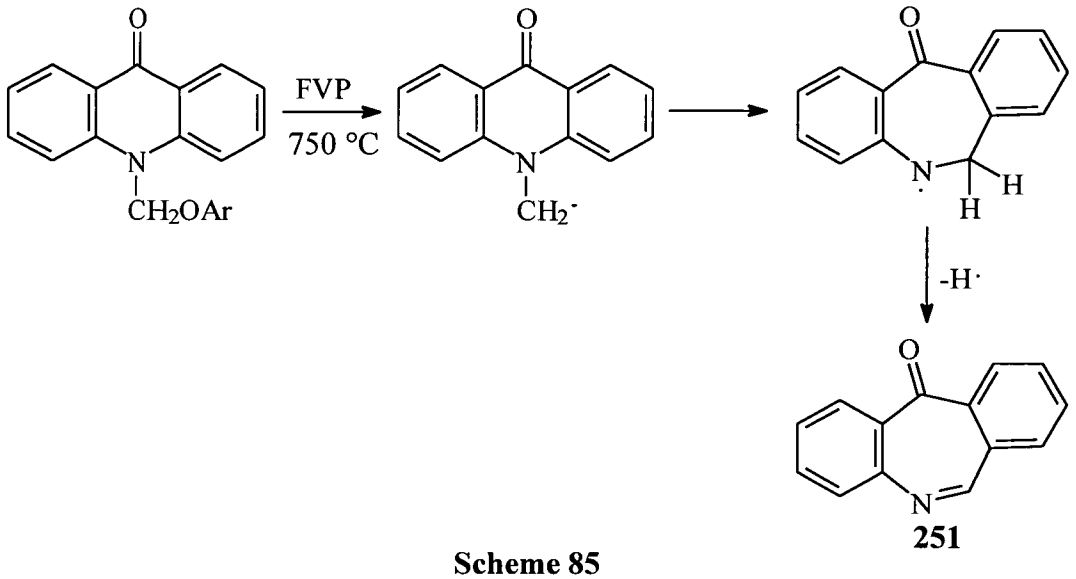


X = Cl, Br

249 **250**

Scheme 84

However, further work by McNab *et al*[71] has shown that the dibenzazepinone **251** can be obtained in low yield using FVP methodology, as shown in **Scheme 85**. This product is known to be stable and isolable at room temperature.[72]



251

Scheme 85

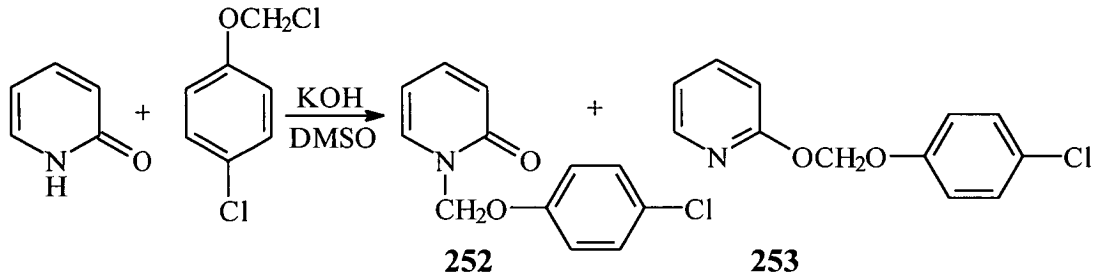
The logical extension of this work was to investigate simpler six-membered heterocycles to determine if they undergo similar ring expansion reactions to yield the appropriate azepinones. The work by Dunkin *et al*[70] suggests that these products may be unstable, and therefore may decarbonylate under FVP conditions at 750 °C. However, the results of Dunkin[70] and McNab[71] suggest that there is an island of stability for these seven-membered compounds. This is suggested by the unstable nature of compound **250** at room temperature and the stability of the dibenzocompound **251** under pyrolysis conditions at 750 °C. Therefore, a series of *N*-(4-chlorophenoxymethyl) substituted heterocyles, namely pyridinones, quinolinones and phenanthridinone, were studied so that this island of stability could be investigated. (It should be noted that these carbonyl containing compounds were used, and not, for example, pyridine itself, as when alkylated, pyridine forms a salt which cannot be pyrolysed)

The 1*H*-pyridin-4-one and 1*H*-pyridin-2-one (and corresponding quinolinones) were studied to see if the position of the carbonyl group would have any effect on the outcome of the pyrolysis reactions.

2.3 Alkylation Reactions.

2.3.1 Synthesis of *N*-(4-chlorophenoxy)methyl heterocycles and *O*-(4-chlorophenoxymethyoxy) heterocycles.

A variety of carbonyl containing heterocycles were subjected to alkylation using α,4-dichloroanisole under basic conditions in DMSO. This is an extension of the Heaney and Ley[73] method for the alkylation of indoles and pyrroles to the six-membered ring systems. The general reaction for 1*H*-pyridin-2-one is shown in **Scheme 86**.



252 **253**

Scheme 86

In every case, the reaction resulted in the formation of two isomers, the *O*-alkylated and the *N*-alkylated products. [The assignment of these isomers is discussed in the next section] A summary of the products formed and their corresponding yields is shown in **Table 9**.

In all reactions, except that for the 1*H*-pyridin-4-one, the *N*-alkylated isomer was the major product. The two isomers can be separated easily by dry flash chromatography, with elution of the *O*-alkylated isomer occurring first in every case.

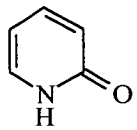
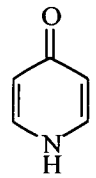
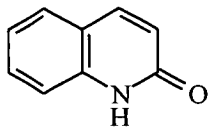
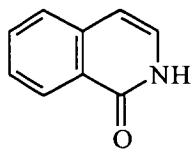
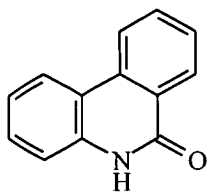
Heterocycle	Compound No., *N*-alkylated	Compound No., *O*-alkylated
	**252**; 31%	**253**; 20%
	**254**; 0%	**255**; 43%
	**256**; 38%	**257**; 32%
	**258**; 48%	**259**; 21%
	**260**; 32%	**261**; 24%

Table 9:- The yields of *N*- and *O*-alkylated isomers obtained in the alkylation reaction of various heterocycles.

An alternative method was required for the synthesis of the *N*-alkylated isomer of the 1*H*-pyridin-4-one. When this compound is considered in terms of the relative hardness and softness of Lewis acids and bases. A "soft" base which would favour attack at the "softer" nitrogen centre is required, rather than the "harder" oxygen atom. Also, changing the solvent from "hard" DMSO to a "softer" one would favour attack at the nitrogen centre.[74]

The following method was devised and the heterocycle was treated with an excess of sodium hydride in THF, then heated to reflux with α,4-dichloroanisole for several hours. This method was used to synthesise the *N*-alkylated isomers of 1*H*-pyridin-4-one and 1*H*-quinolin-4-one. A summary of these reactions is shown in

Table 10. These conditions were not used for the other heterocycles shown in **Table 9**, and in retrospect may produce a higher yield of the *N*-alkylated isomers.

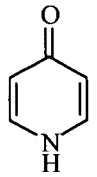
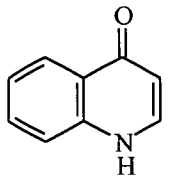
Heterocycle	Compound No., *N*-alkylated	Compound No., *O*-alkylated
	**254**; 35%	**255**; 12%
	**262**; 66%	**263**; 15%

Table 10:- The yields of *N*- and *O*-alkylated isomers obtained in the alkylation reactions of some heterocycles.

2.3.2 Identification of isomers.

There are several different methods available in which the *N*-alkylated and *O*-alkylated isomers could be distinguished. If infrared spectroscopy is used, the *N*-alkylated heterocycles would have a strong characteristic absorption of the carbonyl group in the 1600 - 1700 cm^{-1} range of the spectrum. This would be absent in the spectrum of the corresponding *O*-alkylated isomer. However, for the larger systems, the infrared spectra of the corresponding *N*-alkylated and *O*-alkylated systems did not contain differences that were significant enough for unambiguous assignments to be made. For example, the ν_{max} value for compounds **261** and **260** are 1641.3 cm^{-1} and 1650.3 cm^{-1} respectively. In the proton NMR spectrum, the chemical shift of the methylene group in the *N*- and *O*-alkylated derivatives was not significantly different, and therefore unambiguous identification could not be made from these values alone. For example, the proton chemical shift for this methylene group in compounds **252** and **253** is 5.85 and 6.05 ppm respectively. Therefore, all the compounds were subjected to nOe experiments with irradiation at the methylene group in order to distinguish between the isomers.

NOE spectrum for compound **253**.

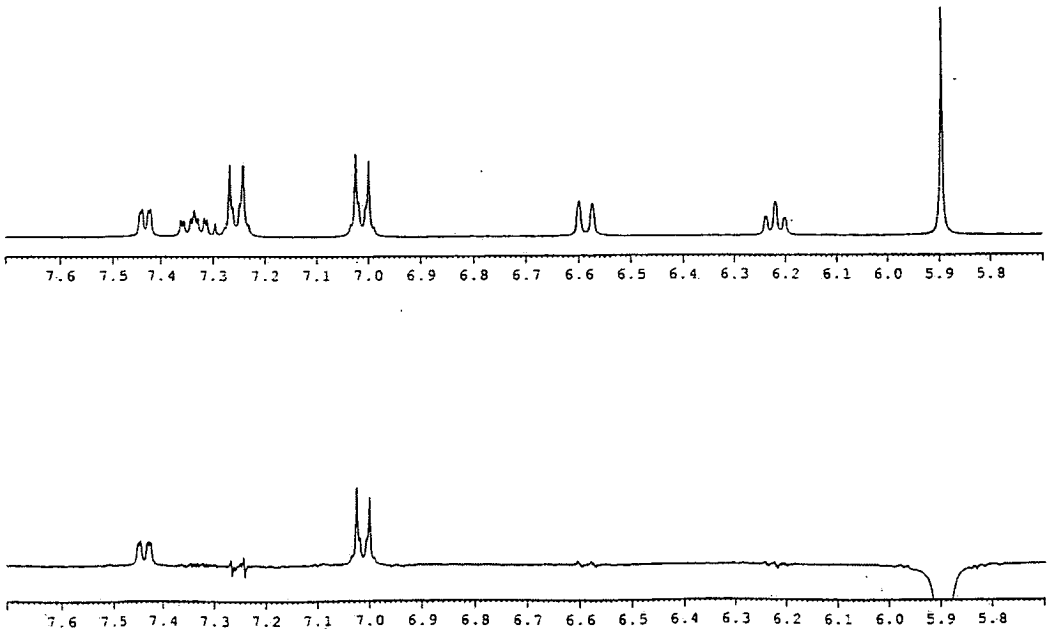
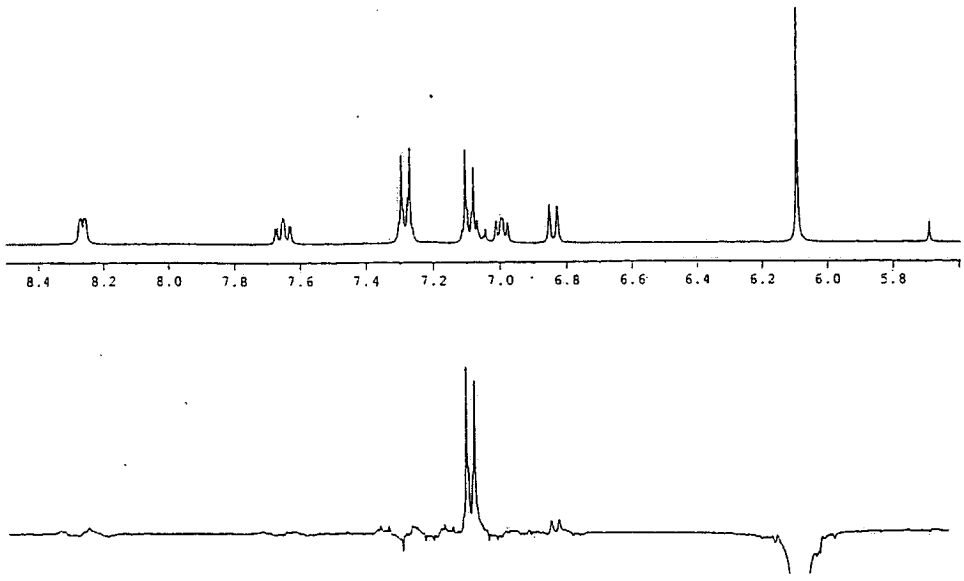


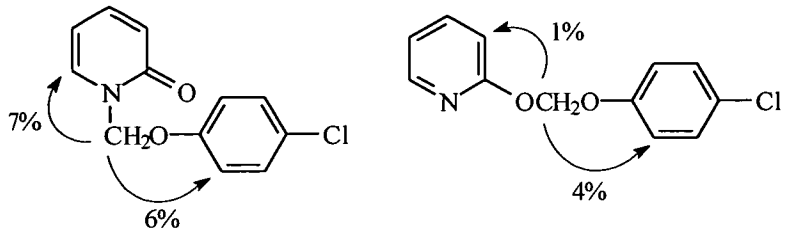
Figure 2

NOE spectrum for compound **254**.



The nOe spectra for compounds **252** and **253** are shown in **Figures 2** and **3** respectively. These spectra are discussed in detail, and the salient features of the other pairs of compounds are discussed to avoid repetition.

The nOe enhancements for compounds **252** and **253** are shown in **Figure 4**.



252 **253**

Figure 4

The nOe spectrum for compound **252** shows the enhancements of two signals at 7.01 and 7.43 ppm, by 6% and 7% respectively. The peaks at 7.01 ppm were assigned as the two *p*-chlorophenyl protons, as they occur in the chemical shift range 6.95 - 7.25 ppm. This is where these protons usually occur, and this signal also displays the characteristic *ortho* couplings of a *para* substituted benzene ring. The other enhanced signal occurred at 7.43 ppm which was assigned as the 6-proton of the pyridinone ring. The chemical shift of the 6-proton in 1-methylpyridin-2-one is 7.22 ppm. This suggests that this is the *N*-alkylated isomer.[75]

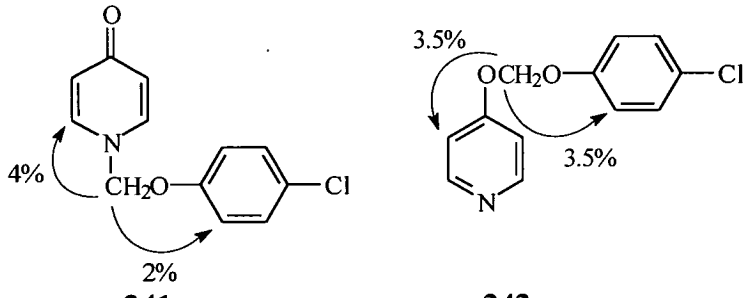
The nOe spectrum for compound **253** shows the enhancement of two signals at 7.08 and 6.83 ppm by 4% and 1% respectively. The enhancement at 7.08 ppm was assigned as the *p*-chlorophenyl protons, as discussed above. The other enhanced signal was assigned as the 3-position of the pyridine ring. This was because it has a chemical shift of 6.83 ppm and the 3-proton in 2-propoxypyridine also occurs at 6.83 ppm. This suggested that this was the *O*-alkylated isomer.[76]

In all the following compounds, the enhanced signal, which occurred in the chemical shift range of 6.95 - 7.25 ppm and showed the characteristic *ortho* couplings of a *para*-substituted aryl compound, was assigned as the *p*-chlorophenyl protons. This is not discussed again.

The nOe enhancements for compounds **241** and **242** are shown in **Figure 5**. In the nOe spectrum for compound **241**, the second enhancement occurred at 7.4 ppm and was assigned as the protons in the 2-position of the pyridinone ring. This corresponds to the chemical shift of the 2-proton in *N*-methylpyridin-4-one which occurs at 7.25 ppm.[77]

In the nOe spectrum for compound **242**, the second enhancement was assigned as the protons in the 3-position of the pyridine ring. This signal was a

doublet with a coupling constant of 4.75 Hz due to coupling with the protons in the 2-position. The coupling constant between the 2- and 3-protons in 4-methoxypyridine is 5.4 Hz which suggests that this is the *O*-alkylated isomer.[78] It should be noted that the coupling constant between the 2- and 3-protons in *N*-methylpyridin-4-one is 8 Hz which is much larger.[77]

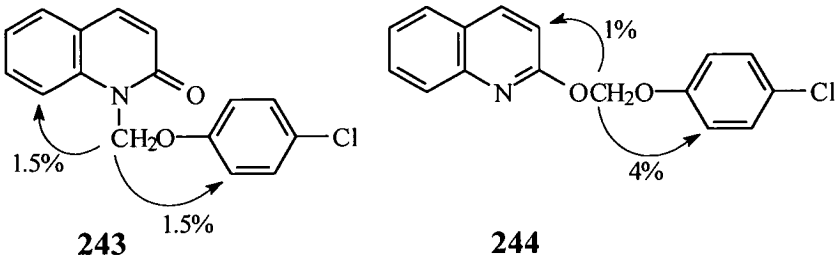


241 **242**

Figure 5

The nOe enhancements for compounds **243** and **244** are shown in **Figure 6**. In the nOe spectrum for compound **243**, the second enhancement was assigned as the proton at the 8-position of the quinolinone ring. This was suggested by the multiplicity of the proton signal due to the *ortho*, *meta* and *para* couplings.

In the nOe spectrum for compound **244**, the second enhancement was assigned as the proton in the 3-position of the quinolinone ring as the signal is a doublet due to its coupling with the proton in the 4-position. This suggests that this is the *O*-alkylated isomer.



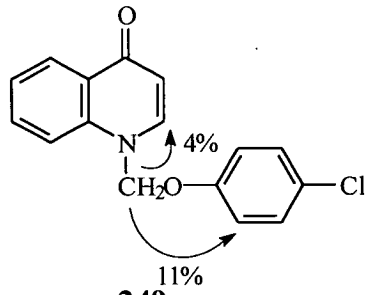
243 **244**

Figure 6

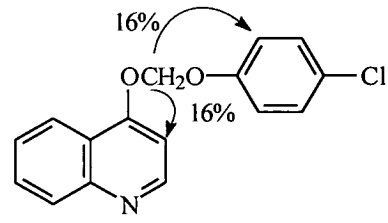
The nOe enhancements for compounds **249** and **250** are shown in **Figure 7**. In the nOe spectrum for compound **249**, the second enhancement was assigned as the proton in the 2-position, as it was a doublet with a coupling constant of 8.1 Hz. The coupling constant between these protons in 1-methylquinolin-4-one is 7.7 Hz.[79] This is much larger than similar coupling constants in the quinoline ring, suggesting that

this is the *N*-alkylated isomer. There was no enhancement of the proton in the 8-position of the quinolinone ring.

In the nOe spectrum for compound **250**, the second enhancement was assigned as the proton in the 3-position of the quinoline ring, as it was a doublet with a coupling constant of 5.2 Hz. This is due to coupling with the proton in the 2-position. This is a smaller coupling constant than observed for these protons in quinolinones. The corresponding coupling constant in 4-methoxyquinoline is 4.6 Hz.[80] This suggests that this compound is the *O*-alkylated isomer.



249

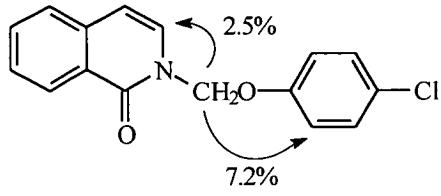


250

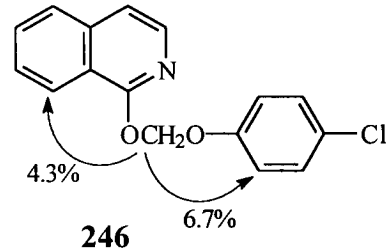
Figure 7

The nOe enhancements for compounds **245** and **246** are shown in **Figure 8**. In the nOe spectrum for compound **245**, the second enhancement was assigned as the proton in the 3-position of the isoquinolinone ring as it was a doublet due to coupling with the proton in the 4-position, suggesting that this was the *N*-alkylated isomer.

In the nOe spectrum of compound **246**, the second enhancement was assigned as the proton in the 8-position of the isquinoline ring. This was suggested by the multiplicity of the signal due to *ortho*, *meta* and *para* couplings suggesting that this was the *O*-alkylated isomer.



245

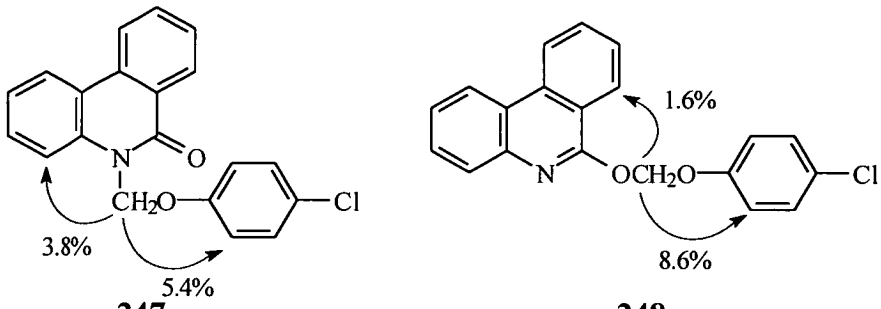


246

Figure 8

The nOe enhancements for compounds **247** and **248** are shown in **Figure 9**. The assignment of compounds **247** and **248** proved more difficult due to the similarity of the protons in the 10- and 3-positions. The elution order from the column suggested the identity of the isomers, with the *O*-alkylated isomer being

eluted first (this pattern was observed for all the pairs of compounds). The similarity of the ^{1}H NMR spectrum of compound **247** to that of 6(5*H*)-phenanthridinone, and of compound **248** to phenanthridine also suggested this assignment.[81]



247 **248**

Figure 9

The structures of compounds **239** and **242** were further confirmed by crystal structures. The structure of compound **239** is shown in **Figures 10** and **11** with the corresponding data in **Tables 11** and **12**. The structure of compound **242** is shown in **Figure 12** with its associated data in **Tables 13** and **14**.

The structure for compound **239** was compared to another *N*-substituted pyridinone, as shown in **Figure 13**.[82]

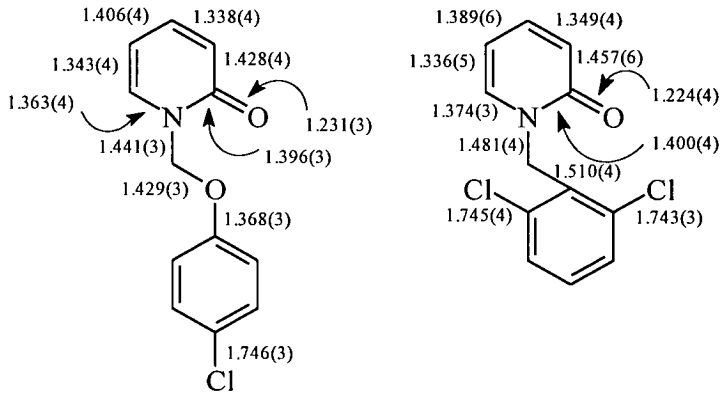


Figure 13

These structures show similar bond lengths around the pyridinone ring, but there is a significant difference in the bond length of the N-C bond. The two C-O bonds in compound **239** have significantly different lengths, with the C-O bond next to the

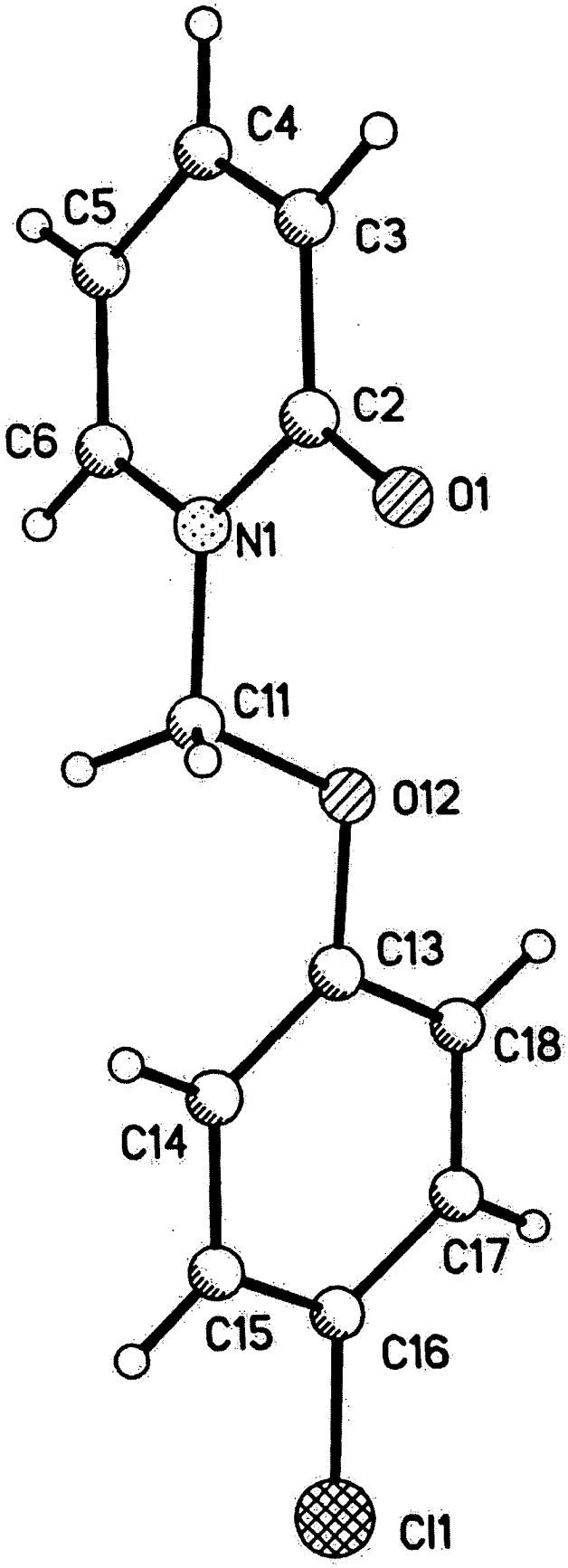


Figure 10

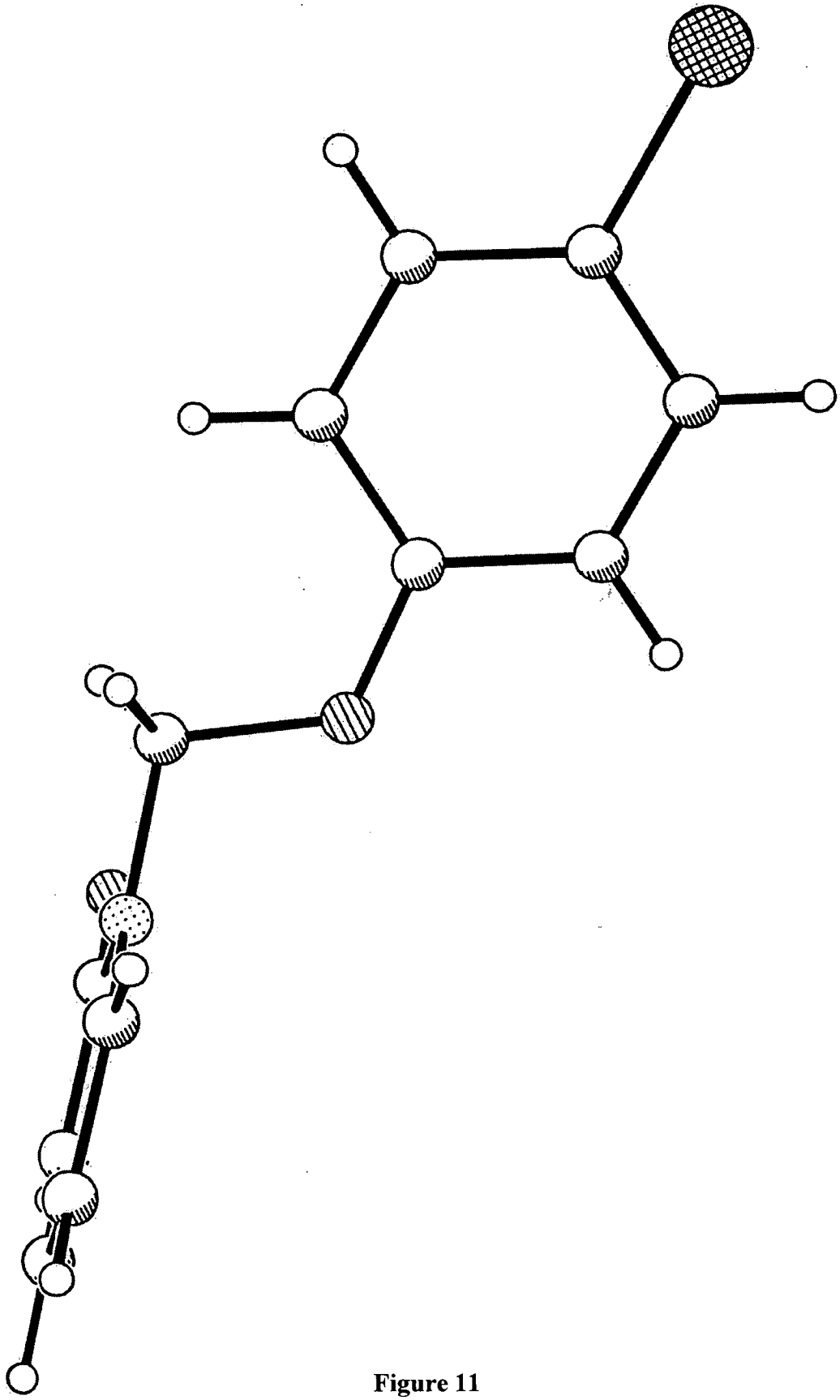


Figure 11

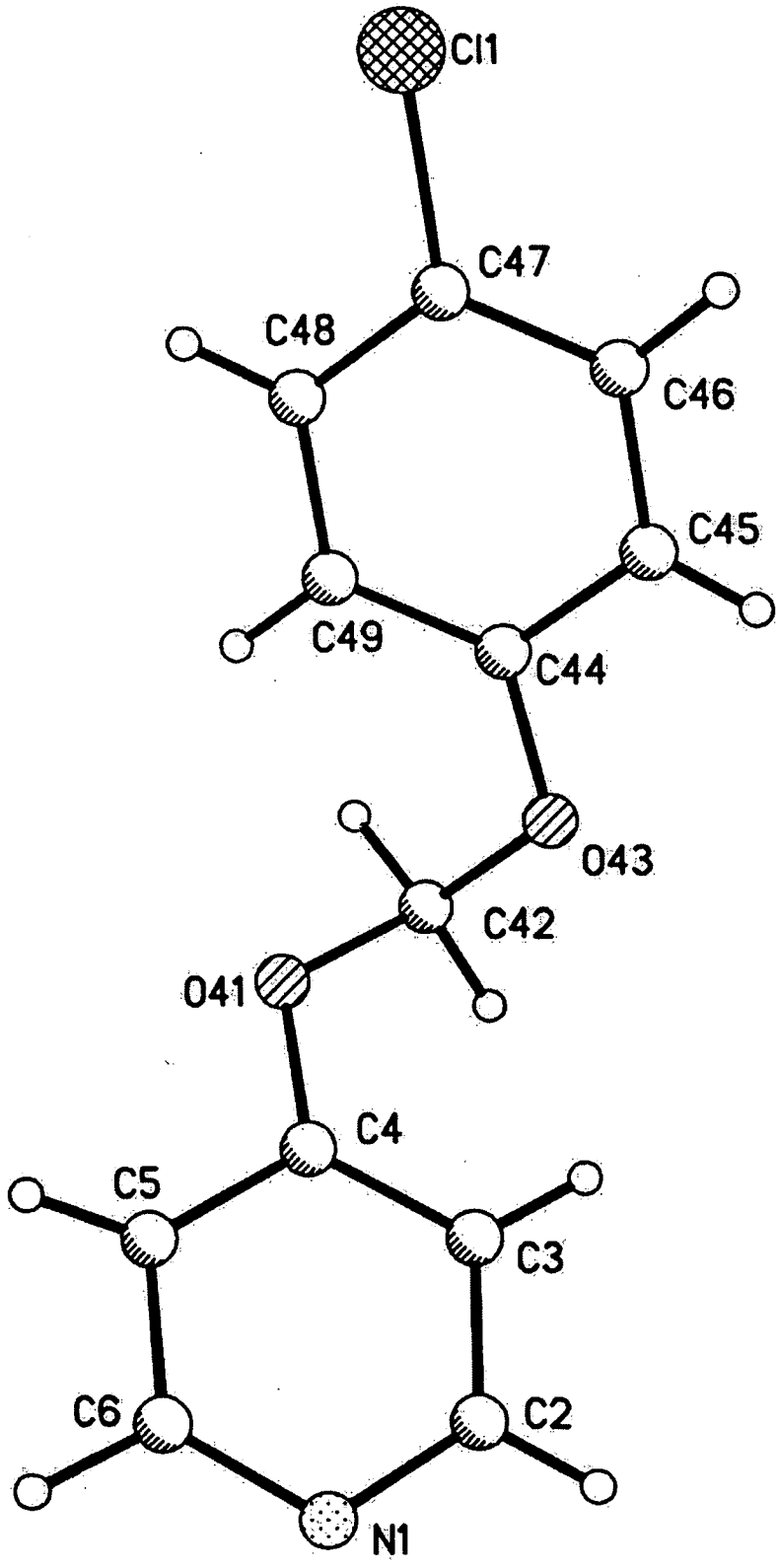


Figure 12

Table 11 Bond Lengths (Å)

O(1) – C(2)	1.231(3)
N(1) – C(6)	1.363(4)
N(1) – C(2)	1.396(3)
N(1) – C(11)	1.441(3)
C(2) – C(3)	1.428(4)
C(3) – C(4)	1.338(4)
C(4) – C(5)	1.406(4)
C(5) – C(6)	1.343(4)
C(11) – O(12)	1.429(3)
O(12) – C(13)	1.368(3)
C(13) – C(14)	1.381(4)
C(13) – C(18)	1.384(4)
C(14) – C(15)	1.385(4)
C(15) – C(16)	1.361(4)
C(16) – C(17)	1.364(4)
C(16) – Cl(1)	1.746(3)
C(17) – C(18)	1.384(3)

Table 12 Bond Angles (degrees)

C(6) – N(1) – C(2)	122.8(3)
C(6) – N(1) – C(11)	118.9(2)
C(2) – N(1) – C(11)	118.2(3)
O(1) – C(2) – N(1)	120.1(3)
O(1) – C(2) – C(3)	125.5(3)
N(1) – C(2) – C(3)	114.4(3)
C(4) – C(3) – C(2)	122.5(3)
C(3) – C(4) – C(5)	120.4(3)
C(6) – C(5) – C(4)	118.7(3)
C(5) – C(6) – N(1)	121.2(3)
O(12) – C(11) – N(1)	107.5(2)
C(13) – O(12) – C(11)	116.4(2)
O(12) – C(13) – C(14)	124.8(3)
O(12) – C(13) – C(18)	115.8(2)
C(14) – C(13) – C(18)	119.4(2)
C(13) – C(14) – C(15)	119.8(3)
C(16) – C(15) – C(14)	119.9(3)
C(15) – C(16) – C(17)	121.1(3)
C(15) – C(16) – Cl(1)	119.8(2)
C(17) – C(16) – Cl(1)	119.1(2)
C(16) – C(17) – C(18)	119.5(3)
C(17) – C(18) – C(13)	120.1(3)

Table 13 Bond Lengths (Å)

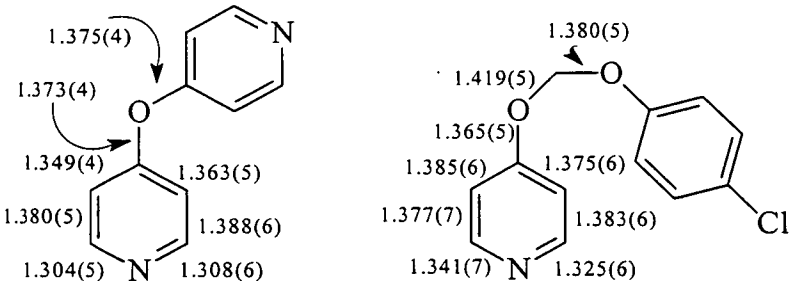
N(1) – C(2)	1.325(6)
N(1) – C(6)	1.341(7)
C(2) – C(3)	1.383(6)
C(3) – C(4)	1.375(6)
C(4) – O(41)	1.365(5)
C(4) – C(5)	1.385(6)
C(5) – C(6)	1.377(7)
O(41) – C(42)	1.419(5)
C(44) – C(45)	1.380(5)
C(44) – C(49)	1.382(6)
C(44) – O(43)	1.384(4)
O(43) – C(42)	1.407(5)
C(45) – C(46)	1.384(5)
C(46) – C(47)	1.379(7)
C(47) – C(48)	1.379(5)
C(47) – Cl(1)	1.740(4)
C(48) – C(49)	1.390(5)

Table 14 Bond Angles (degrees)

C(2) – N(1) – C(6)	115.8(4)
N(1) – C(2) – C(3)	124.8(4)
C(4) – C(3) – C(2)	118.2(4)
O(41) - C(4) – C(3)	125.6(3)
O(41) – C(4) – C(5)	116.0(4)
C(3) – C(4) – C(5)	118.5(4)
C(6) – C(5) – C(4)	118.6(4)
N(1) – C(6) – C(5)	124.0(4)
C(4) – O(41) – C(42)	118.0(3)
C(45) – C(44) – C(49)	120.8(3)
C(45) – C(44) – O(43)	114.8(3)
C(49) – C(44) - O(43)	124.4(3)
C(44) – O(43) – C(42)	117.6(3)
O(43) – C(42) – O(41)	111.1(3)
C(44) – C(45) – C(46)	120.3(4)
C(47) – C(46) – C(45)	118.7(4)
C(46) – C(47) – C(48)	121.4(4)
C(46) – C(47) – Cl(1)	118.9(3)
C(48) – C(47) – Cl(1)	119.8(4)
C(47) – C(48) – C(49)	119.7(4)
C(44) – C(49) – C(48)	119.0(3)

benzene ring displaying more double bond character than the other one. This suggests that the central C-O bond should be weaker and therefore should break under pyrolysis conditions (**Scheme 80**). The phenyl rings also have similar bond lengths, and there is no significant difference in the length of the C-Cl bond whether it is in the *ortho* or *para* position.

Compound **242** was also compared to a 4-substituted pyridine as shown in **Figure 14**.[83]



(a) **(b)**

Figure 14

These compounds have significantly different bond lengths around the pyridine ring with the two N-C bonds in **Figure 14(a)** showing more double bond character than those in **Figure 14(b).**

2.4 Pyrolysis Reactions of *O*-alkylated Pyridines and *N*-alkylated Heterocycles.

The pyrolysis of all the *N*-alkylated isomers were carried out at 750 °C. This was the optimum temperature, with pyrolysis precursor being recovered from the pyrolysate at lower temperatures.

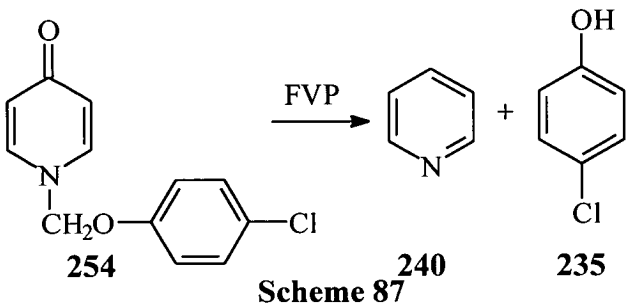
This section is arranged by the course of the pyrolysis reaction and is in three sections. These are i/ Radical Ring Expansion Reactions.

ii/ Carbene Generator Reactions.

iii/ Pyrolysis of *O*-alkylated Pyridines.

2.4.1 Ring Expansion Reactions.

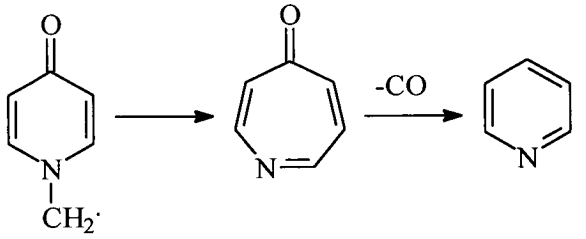
The pyrolysis of compound **254** produced pyridine **240**, and *p*-chlorophenol **235** in yields of 44% and 82% respectively, as illustrated in **Scheme 87**.



254 **240** **235**

Scheme 87

The presence of pyridine was confirmed by a spiking experiment where the pyrolysate was spiked with pyridine, and then subjected to ^{1}H NMR spectroscopy. The spectrum showed that there were no additional peaks on addition of pyridine, but that the integrals of existing (pyridine) peaks had become more intense. A possible explanation for the formation of these products is shown in **Scheme 88**. Initially the 4-oxopyridinemethyl radical **264** undergoes a ring expansion reaction to give seven-membered heterocycle **265**, and decarbonylation of this results in pyridine **240**.

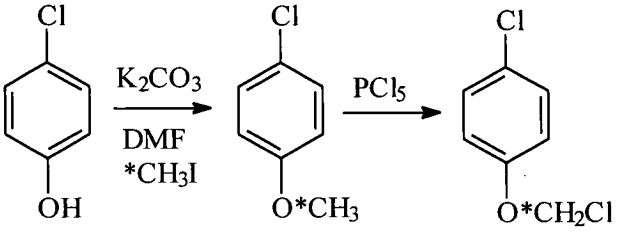


264 **265** **240**

Scheme 88

It should be noted that 1*H*-pyridin-2-one can itself decarbonylate to give pyrrole in low yields, under flow pyrolysis conditions at 960 - 1020 °C.[84]

To probe this mechanism further, ^{13}C labelling methodology was employed. Initially, [7-^{13}C]-α,4-dichloroanisole was synthesised as shown in **Scheme 89**.

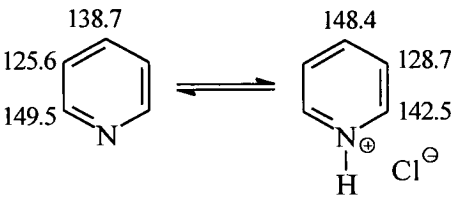


Scheme 89

The second step in this reaction is a scaledown of Gross and Burger's method[85] for α,4-dichloroanisole synthesis which had been optimised by McLellan *et*

al.[86] The labelled *N*-(*p*-chlorophenoxymethyl)pyridin-4-one was then synthesised using the same method as the unlabelled derivative, in 30% yield.

The pyrolysis of this labelled precursor resulted in pyridine with the label present in the 2-position only. This was concluded from the ^{13}C and ^{1}H NMR of the pyrolysate which are shown in **Figures 15** and **16** respectively. The carbon spectrum shows a large peak at 148.90 ppm and this must be due to the carbon label. (It should be noted that the smaller peaks at 130 ppm and 117 ppm are due to the *p*-chlorophenol at natural abundance. The peak at 84 ppm is due to the labelled methylene group of recovered starting material.) The peak due to the carbon label could not be assigned conclusively as the 2-position from the carbon chemical shift alone. This is because there are small amounts of hydrochloric acid produced during the pyrolysis which can protonate the pyridine. An equilibrium is set up between the pyridine and pyridine hydrochloride which is shown in **Scheme 90**.



Scheme 90

The carbon chemical shifts in ppm are shown for each position, and it can be seen that in pyridine, the carbon at the 4-position has a lower chemical shift than the carbon at the 2-position. This is reversed in pyridine hydrochloride.

The proton spectrum shows the signal for one of the protons at the 2-position split into two due to coupling with the carbon label (at ~8.4 and 8.9 ppm) while the signal for the other proton at the 2-position (at 8.65 ppm) remained unchanged. This allowed unambiguous assignment of the position of the carbon label to be made. A proposed mechanism is shown in **Scheme 91**.

^{13}C NMR spectrum of pyrolysate of labelled **254**.

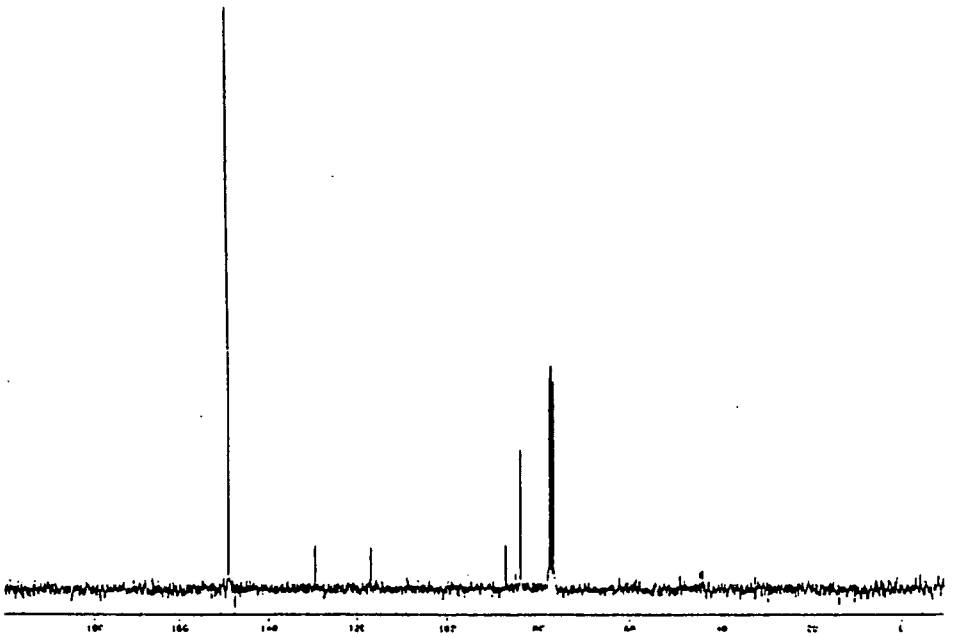


Figure 15

^{1}H NMR spectrum of pyrolysate of labelled **254**.

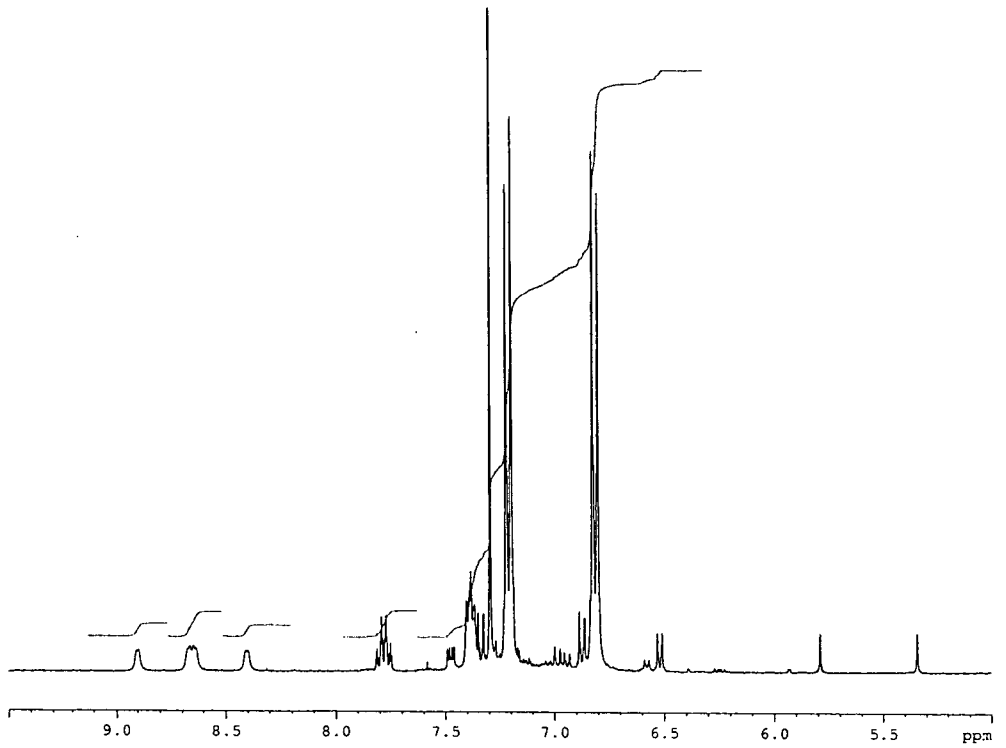
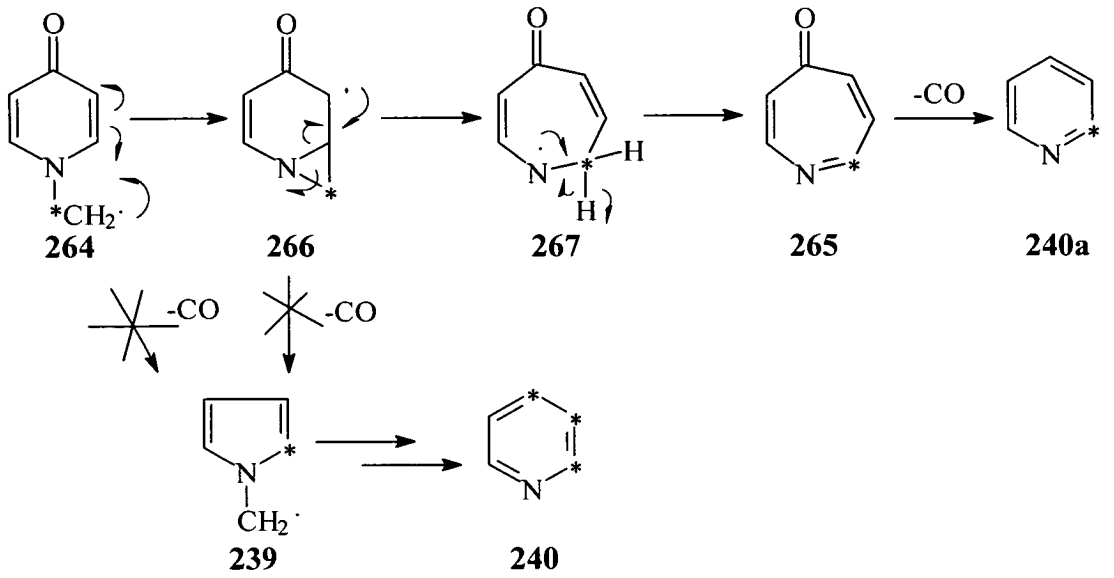


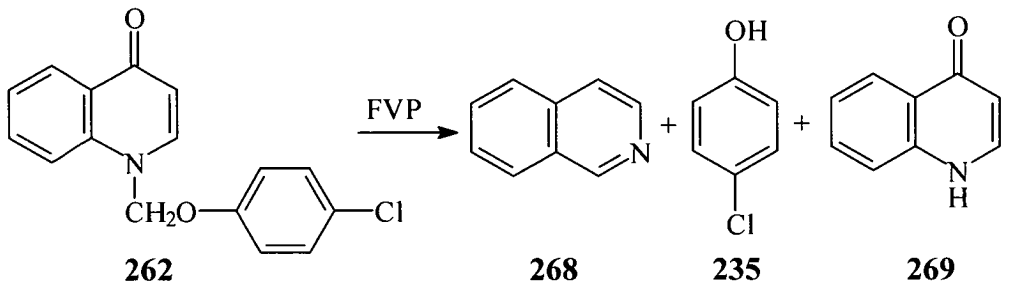
Figure 16



Scheme 91

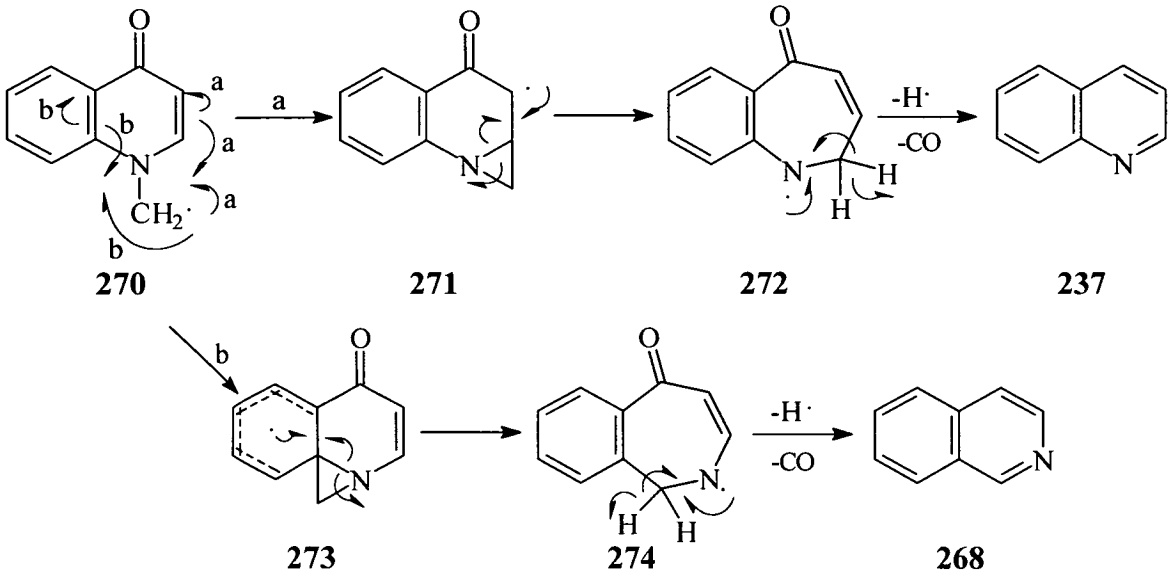
As the label only occurs in the 2-position of the pyridine **240a**, it is thought that the reaction must go through to at least intermediate **267** before decarbonylation takes place. If decarbonylation took place at either of the intermediates **264** or **266** then it would form the known *N*-pyrrolylmethyl radical **239**. This ring expands to give pyridine, with the label occurring at all three positions and with the majority at the 3-position, as shown in **Scheme 82**.[67]

Pyrolysis of compound **262** produced isoquinoline **268**, *p*-chlorophenol **235** and 1*H*-quinolin-4-one **269** in yields of 32%, 82% and 39% respectively, as illustrated in **Scheme 92**.



Scheme 92

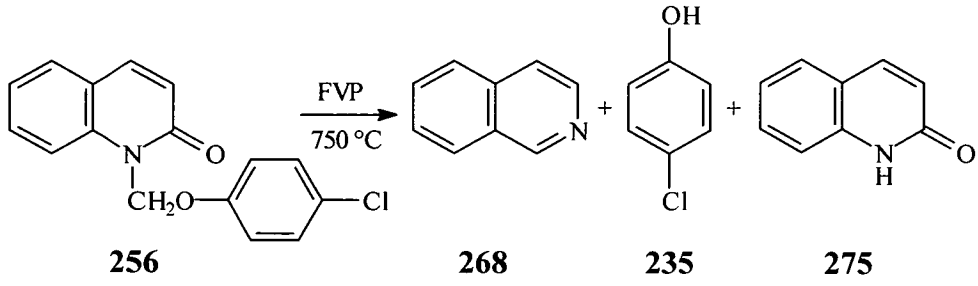
The presence of isoquinoline **268** was confirmed by a spiking experiment. This enhanced the signals assigned to isoquinoline in the ^{1}H NMR spectrum with no new signals appearing. Isoquinoline could be present due to a ring expansion reaction, followed by decarbonylation. A proposed mechanism is shown in **Scheme 93**.



Scheme 93

The 4-oxyquinolinemethyl radical **270** has two pathways open to it. If pathway "a" is followed, the radical will attack at the double bond of the non-aromatic ring, to form a three-membered ring **271**. This will open due to ring strain to give the seven-membered ring **272**, and decarbonylation results in quinoline **237**. If pathway "b" is followed, the radical attacks at the phenyl ring to give a three-membered ring **273**. As before this will ring open to give the seven-membered ring **274**, and decarbonylation results in isoquinoline **268**. The presence of isoquinoline in the pyrolysate suggests that pathway "b" is followed. It should be noted that in this case, the attack is exclusively in the direction of the phenyl ring. This is in direct contrast to the indolyl derivative, shown in **Scheme 81**, where the attack is exclusively at the 2-position of the indole ring. This suggests that intermediate **273** is more stable than enolyl radical **271** under gas phase conditions. The unexpected presence of compound **269** in the pyrolysate is discussed in the next section.

Pyrolysis of compound **256** resulted in isoquinoline **268**, *p*-chlorophenol **235** and 1*H*-quinolin-2-one **275** in yields of 22%, 80% and 54% respectively, as shown in **Scheme 94**.

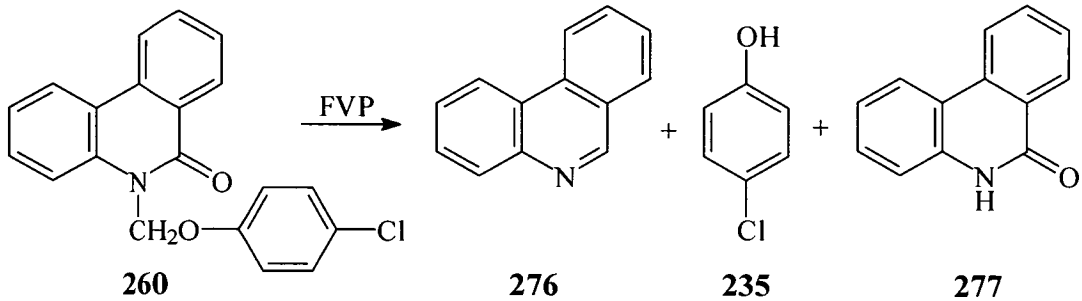


256 **268** **235** **275**

Scheme 94

Again, isoquinoline can be derived from the decarbonylation of a ring expansion product, *via* a similar mechanism as for compound **262**. Again, attack next to the phenyl group seems to be favoured, and as before the unexpected presence of compound **269** in the pyrolysate will be discussed in the next section.

Pyrolysis of compound **260** produced phenanthridine **276**, *p*-chlorophenol **235** and 1*H*-phenanthridin-6-one **277** in yields of 42%, 77% and 10% respectively, as shown in **Scheme 95**.



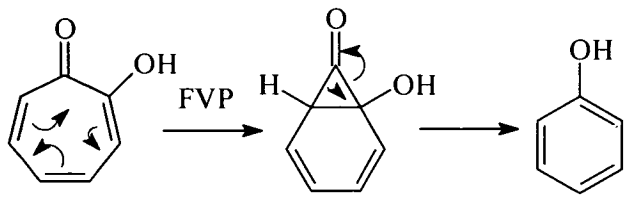
260 **276** **235** **277**

Scheme 95

The presence of phenanthridine **276** in the pyrolysate suggests that a ring expansion reaction followed by decarbonylation has occurred. The oxophenanthridinemethyl radical can insert at the phenyl ring or next to the carbonyl group, and in each case phenanthridine **276** would be the product after decarbonylation. Therefore the pathway cannot be completely defined from these observations. However, the insertion mechanism of the two quinolinones suggests that insertion at the phenyl ring is most likely. The unexpected presence of compound **277** in the pyrolysate is discussed in the next section.

The results discussed so far suggest that decarbonylation plays a major role in which products are formed. Therefore an analogous carbocyclic structure **278**, to the targeted azepinone system was subjected to flash vacuum pyrolysis conditions at

temperatures of 650 - 850 °C to investigate its decarbonylation patterns. Tropolone was chosen as a suitable precursor, and it should decarbonylate to give phenol as shown in **Scheme 96**. The relative yields of each at various temperatures are illustrated in **Graph 1**.

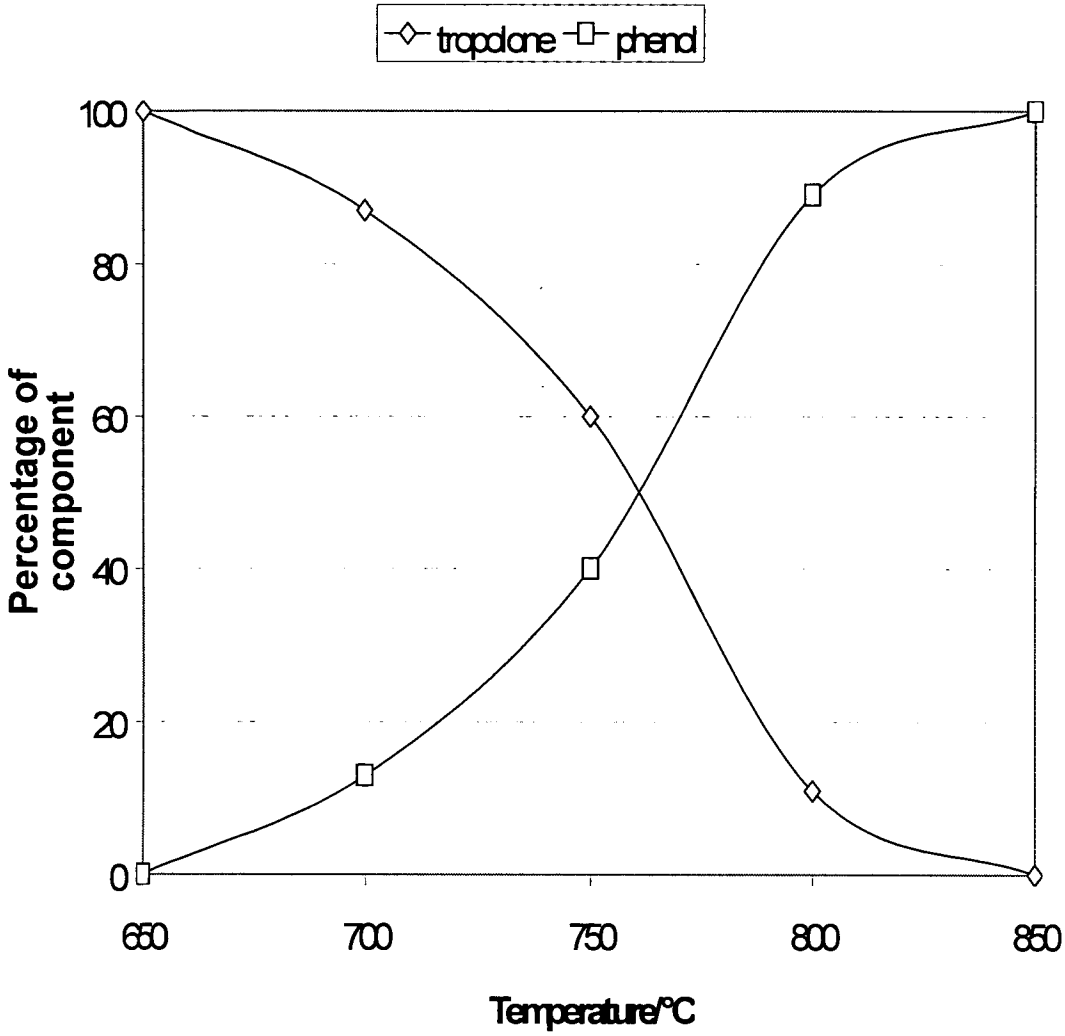


278

Scheme 96

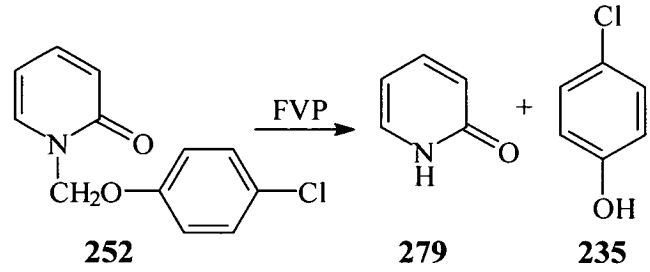
The following graph shows that under FVP conditions, 100% of tropolone survives at 650 °C, but by ~780 °C, more than 50% has undergone decarbonylation. At 850 °C, 100% of the tropolone has undergone decarbonylation. These observations suggest that at the pyrolysis temperatures used for the radical ring expansion reactions, decarbonylation could take place if the seven-membered heterocycles were being formed.

Graph 1 - Decarbonylation of Tropolone.



2.4.2 Carbene Generator Reactions.

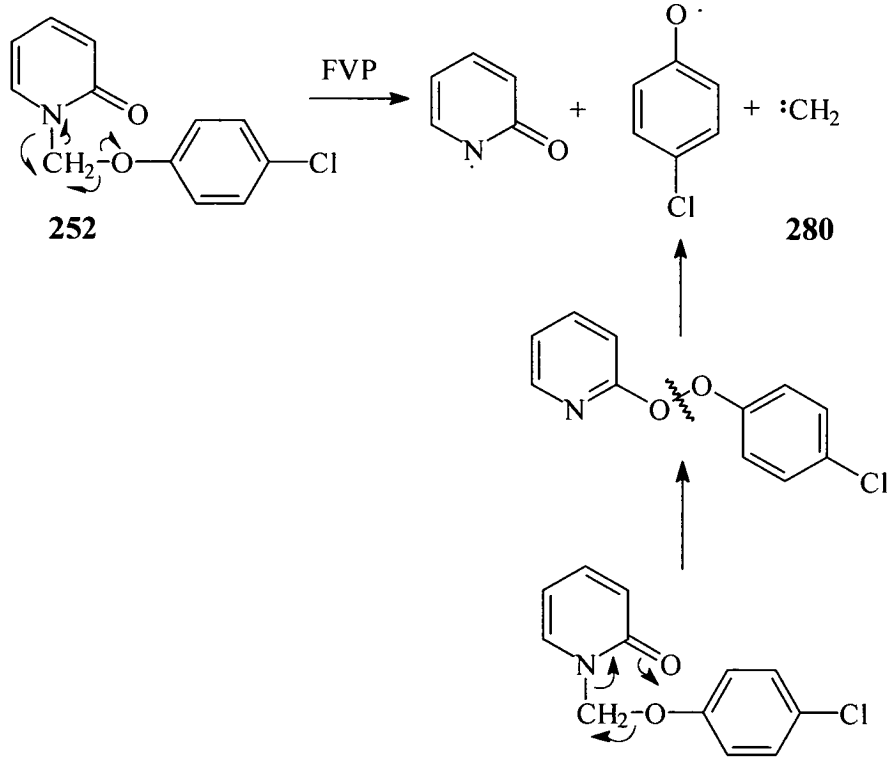
The pyrolysis of compound **252** resulted in *p*-chlorophenol **235** and 1*H*-pyridin-2-one **279** in high yield, as shown in **Scheme 97**.



252 **279** **235**

Scheme 97

This result was unusual, as the methylene group in the precursor is not accounted for in the products. As compound **252** did not produce a ring expansion product and compound **254** did, it suggested that there was a different mechanism occurring when the carbonyl position is in the 2-position (**252**) and when it occurs in the 4-position (**254**). One possible explanation for this, is that compound **252** is acting as a carbene generator as shown in **Scheme 98**.



252 **280**

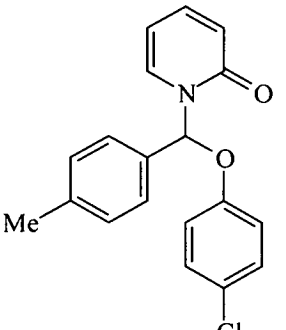
Scheme 98

The only products that would be seen in the pyrolysate, are compounds **279** and **235**. The carbene **280** would rearrange to form ethylene, which would be lost under the

work-up procedures in a FVP experiment. However, the difference in pyrolysis behaviour of compounds **252** and **254** suggests that the standard homolysis in **252** is diverted by a lower energy intramolecular mechanism. One possibility might be intramolecular phenoxy group transfer with concomitant carbene formation, as shown in **Scheme 98**.

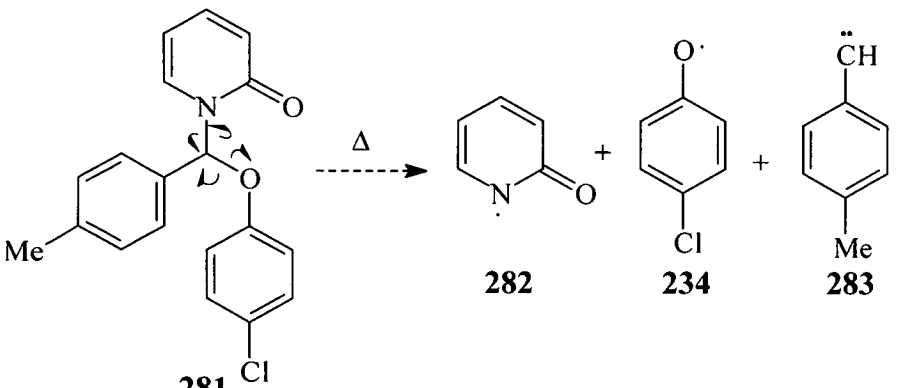
In order to investigate this, a compound that would generate a carbene with a distinctive breakdown pattern was required. This would allow the identification of the intermediate if a carbene instead of a radical was formed.

Compound **281** became a target compound.



281

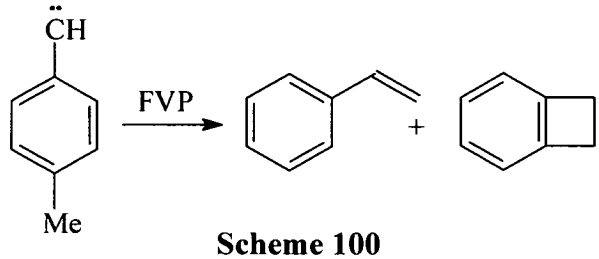
When subjected to FVP conditions, it was thought that compound **281** would result in the radicals **282**, **234** and the carbene **283**, as shown in **Scheme 99**.



281 **282** **234** **283**

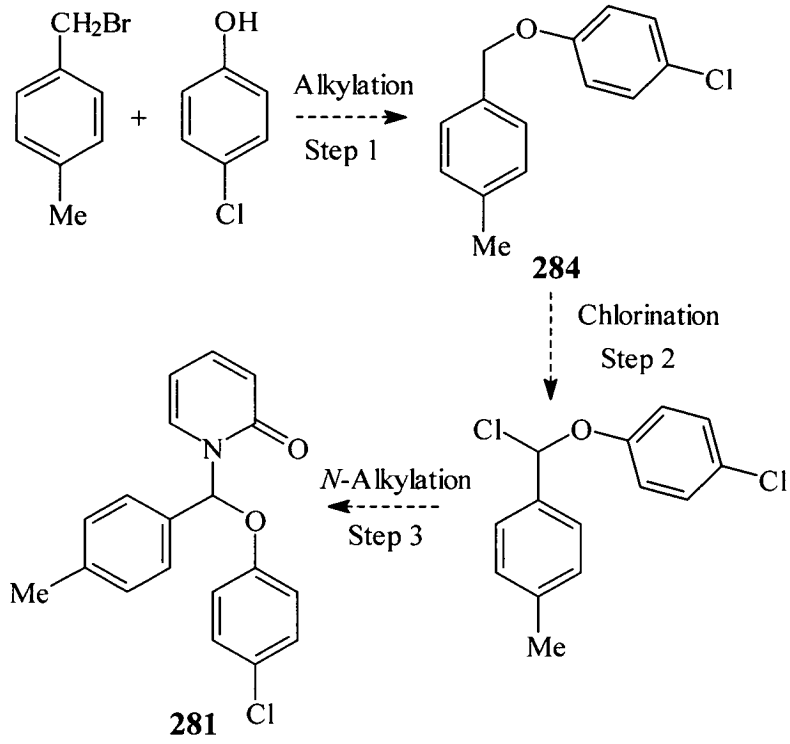
Scheme 99

The expected products would therefore be the 1*H*-pyridin-2-one, *p*-chlorophenol and the tolyl carbene **283**. The tolyl carbene has a distinctive rearrangement pattern and is known to give styrene and benzylcyclobutene, as shown in **Scheme 100**.[87, 88]



Scheme 100

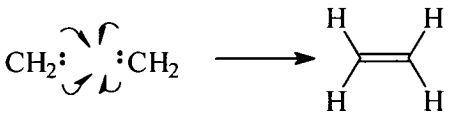
The suggested synthesis of compound **281** is shown in **Scheme 101**.



Scheme 101

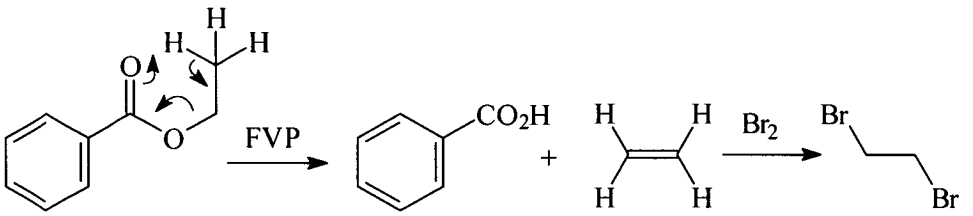
The initial alkylation step (Step 1) was carried out under standard K_2CO_3/DMF alkylation conditions and compound **284** was obtained in 63% yield. However, attempts to chlorinate compound **284** using both PCl_5 and $SOCl_2$ under standard conditions resulted in the recovery of starting materials and no desired product. Therefore, an alternative method to identify the presence of a carbene was sought.

If a carbene was produced, it is likely that it would dimerise in the vacuum system of the FVP apparatus, and in this case would result in ethylene as shown in **Scheme 102.**



Scheme 102

Ethylene is a gas, and the normal FVP work-up procedures would not trap this, explaining its absence in the pyrolysate. Therefore, a new trapping system was designed so that the ethylene could be trapped if it was produced. In this set-up, two U-tubes were used in series (both cooled with liquid nitrogen) with bromine in [^{2}H]-chloroform distilled into the U-tube nearest the pump. This distillation was carried out with the entire system held under vacuum. The pyrolysis experiment was carried out as normal and when complete, the liquid nitrogen was removed from the trap near the furnace, but left around the trap near the pump whilst the first trap warmed to room temperature. The liquid nitrogen was then removed from the second trap, and the experiment was worked up as for other FVP experiments. The contents of the second trap only, were analysed by ^{1}H and ^{13}C NMR spectroscopy as the contents of the first trap have already been discussed. (see **Section A2.4.2**). If ethylene was present, it would react with the bromine *in situ* to form 1,2-dibromoethane, which could be detected by ^{1}H and ^{13}C NMR spectroscopy and subsequent comparison to literature spectra.[81] To test this, ethyl benzoate was pyrolysed using this trapping system as it is known to give ethylene under these conditions, as shown in **Scheme 103.**

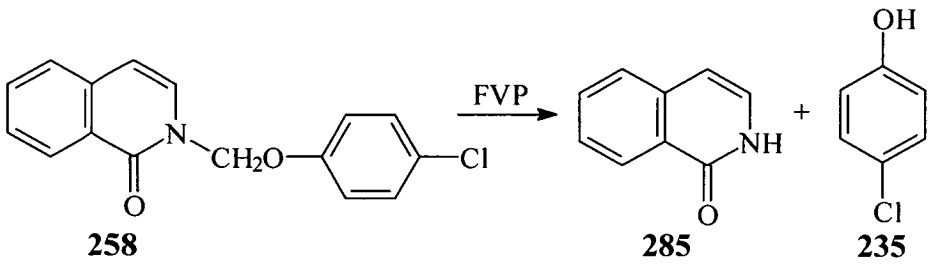


Scheme 103

1,2-Dibromoethane was identified as the sole product in the second trap from this pyrolysis by comparison to literature ^{1}H and ^{13}C NMR spectra.[81]

Compound **252** was pyrolysed using this trapping method and 1,2-dibromoethane was identified in the pyrolysate of the second trap. This suggests that compound **252** is indeed acting as a carbene generator, as shown in **Scheme 98**.

When compound **258** was pyrolysed, it resulted in isocarbostyril and *p*-chlorophenol in high yield, as shown in **Scheme 104**.



258 **285** **235**

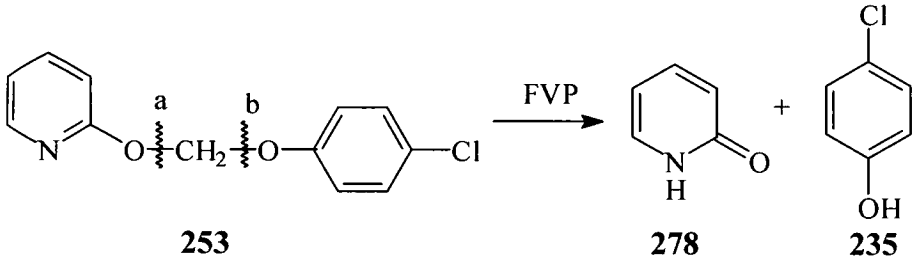
Scheme 104

Again, the methylene group in compound **258** is unaccounted for in the pyrolysate. This suggests that compound **258** also acts as a carbene generator under these conditions.

The pyrolysis of compounds **262**, **256** and **260** shown in **Schemes 92**, **94** and **95** respectively, all have the parent heterocycle in the pyrolysate. This suggests that these precursors can either ring expand as discussed in **Section A2.4.1** or can act as carbene generators as discussed above. These are competing reactions and hence the pyrolysate contains products from both reaction pathways.

2.4.3 Pyrolysis of *O*-Alkylated Pyridines.

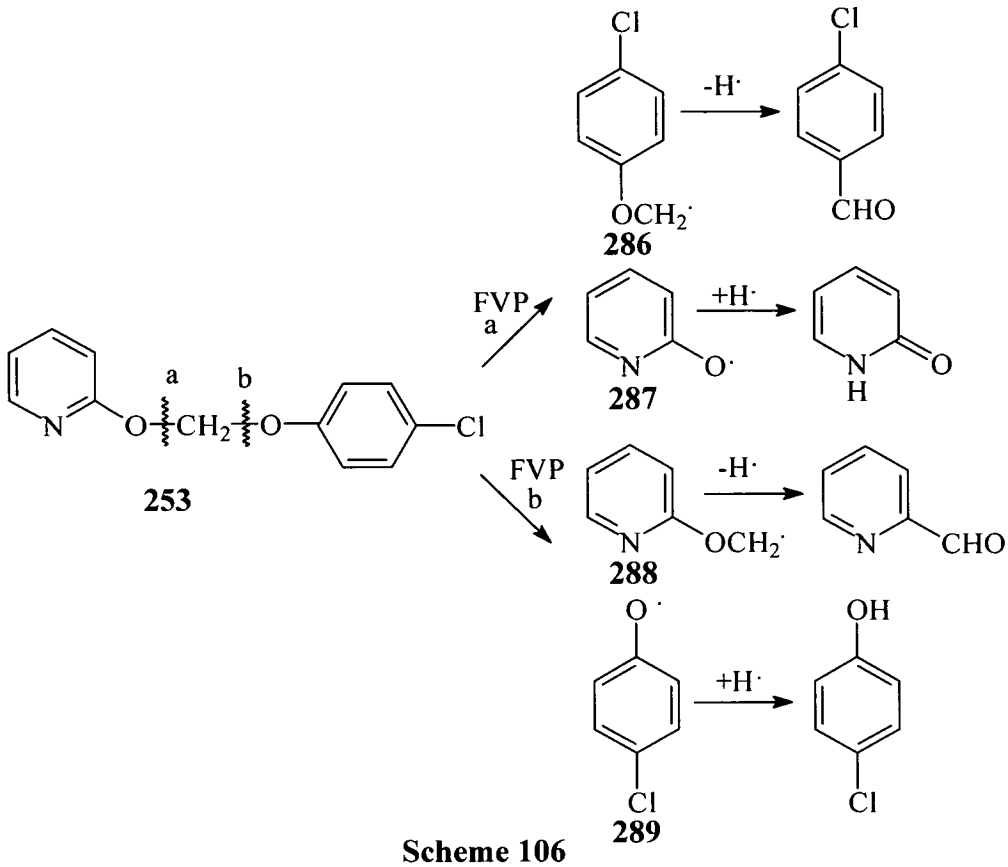
As the *O*-alkylated isomers were also produced in the alkylation reactions, some of these were also subjected to flash vacuum pyrolysis conditions to investigate their behaviour. The pyrolysis of compound **239** resulted in the formation of *p*-chlorophenol **235** and 1*H*-pyridin-2-one **278** in high yields, as shown in **Scheme 105**.



253 **278** **235**

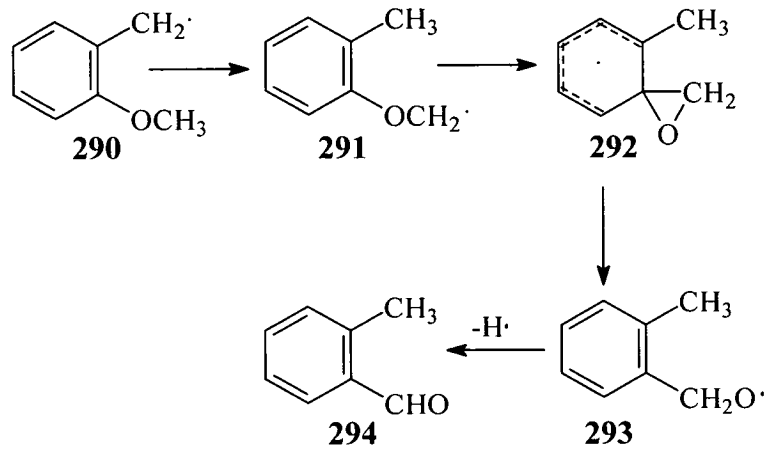
Scheme 105

These proved to be unusual results, as illustrated in **Scheme 106**.



Scheme 106

If bond "a" breaks during the pyrolysis, then radicals **286** and **287** would be produced, and these would yield *p*-chlorobenzaldehyde and 1*H*-pyridin-2-one respectively. The arrangement of R-OCH_2 radicals to aldehydes has been rationalised by De Mayo[89] and later by McNab[90], as shown in **Scheme 107**.



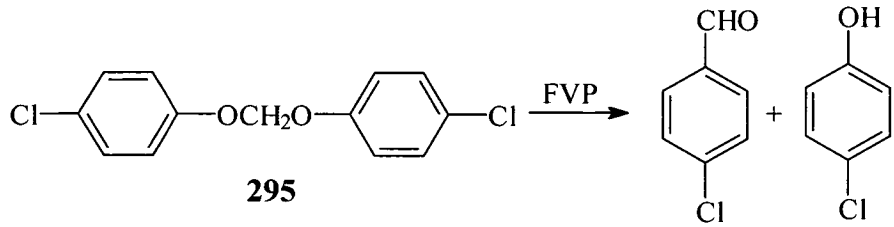
Scheme 107

In **290**, the methylene radical abstracts a proton from the neighbouring methoxy group, resulting in intermediate **291**. This radical forms a three-membered ring by

breaking the aromaticity of the benzene ring **292**. The three-membered ring then breaks in the opposite sense to form an oxygen centred radical **293**. The loss of a hydrogen atom forms aldehyde **294**.

If bond "b" breaks in compound **253** (**Scheme 106**), radicals **288** and **289** would be formed, which would yield pyridine-2-carboxaldehyde and *p*-chlorophenol respectively.

Neither of the expected aldehydes were produced, which suggested that the aldehydes were not stable, or that they were undergoing an alternative reaction under FVP conditions. To investigate this, compound **295** was chosen as a suitable precursor. It was thought that when pyrolysed, this compound would result in *p*-chlorophenol and *p*-chlorobenzaldehyde, as shown in **Scheme 108**.

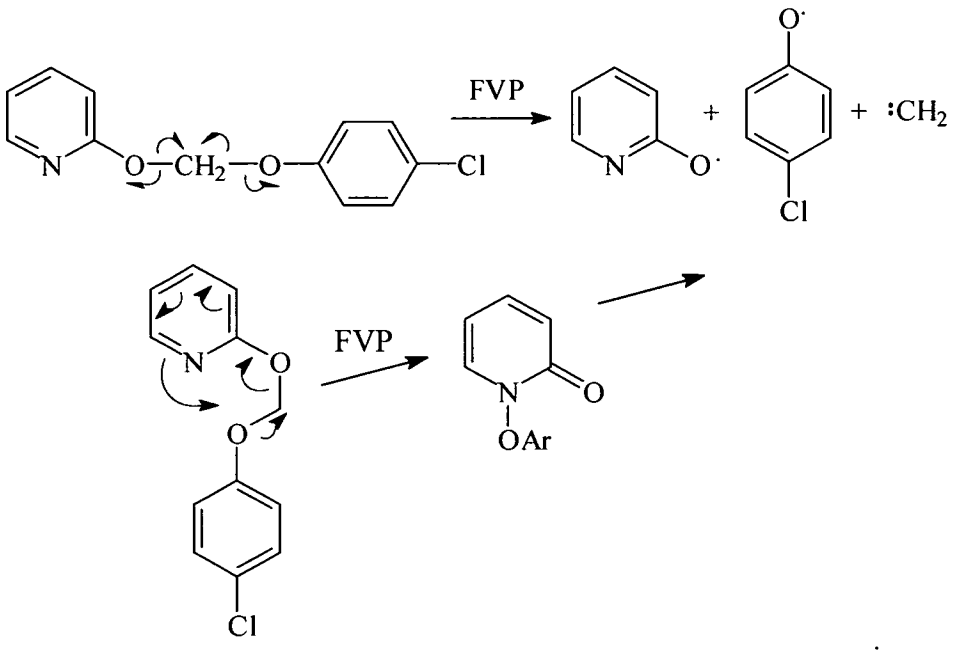


295

Scheme 108

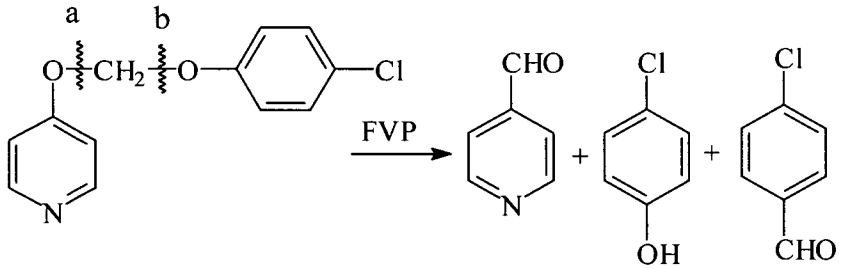
Compound **295** was synthesised using standard DMF/K_2CO_3 alkylation conditions and was produced in high yield. The pyrolysis of this compound at 750 °C resulted in *p*-chlorophenol in 66% yield and *p*-chlorobenzaldehyde in 34% yield (from ^1H NMR spectroscopy). This suggests that the *p*-chlorobenzaldehyde is stable and that the rearrangement to the aldehyde does occur in reasonable yields under these conditions. Therefore this unusual result must be due to an alternative mechanism occurring in this pyrolysis reaction.

Compound **240** was then pyrolysed using the bromine trapping method described in **Section A2.4.2**. Again, 1,2-dibromoethane was identified in the pyrolysate of the second U-tube in series. This suggests that compound **240** also acts as a carbene generator, as shown in **Scheme 109**. This also shows that an intramolecular rearrangement could take place which could explain the differences in the pyrolysis behaviour of the 2-substituted compounds and the 4-substituted compounds.



Scheme 109

Pyrolysis of compound **255** resulted in the formation of *p*-chlorophenol **235**, *p*-chlorobenzaldehyde **297** and pyridine-4-carboxaldehyde **296** in yields of 84%, 7% and 40% respectively, as shown in **Scheme 110**.



255 **296** **235** **297**

Scheme 110

As the major products in the pyrolysis were *p*-chlorophenol and pyridine-4-carboxaldehyde, it can be inferred that bond "b" breaks predominantly. The trace amount of *p*-chlorobenzaldehyde suggests that bond "a" also breaks under these conditions, but there is no presence of the 1*H*-pyridin-4-one which would be expected from this bond breakage. This may not be entirely unexpected, as the crystal structure of this compound (**Figure 12**) shows that bond "b" is longer than bond "a" and will therefore be weaker and more likely to break under pyrolysis conditions.

Flash vacuum pyrolysis (FVP) reactions of *N*-(4-chlorophenoxymethyl)pyridinone systems and their benzo-fused analogues were found to follow one of two pathways. The first pathway was followed by the pyridin-4-one, phenanthridinone, quinolin-2-one and quinolin-4-one systems which all gave the parent heterocycle (*i.e.* pyridine, phenanthridine or quinoline respectively). This occurred by a ring expansion reaction to the seven-membered heterocycle, which was unstable under pyrolysis conditions and spontaneously decarbonylated to give the parent heterocycle. The ring expanded azepinones have been confirmed as intermediates by ^{13}C labelling experiments. The second pathway was followed by the pyridin-2-one and isocarbostyril systems where *p*-chlorophenol and the initial heterocycle (*i.e.* pyridin-2-one or isocarbostyril respectively) were obtained. The 'missing' CH_2 group was detected as ethylene by bromine trapping experiments, which suggests that these compounds act as carbene generators under pyrolytic conditions.

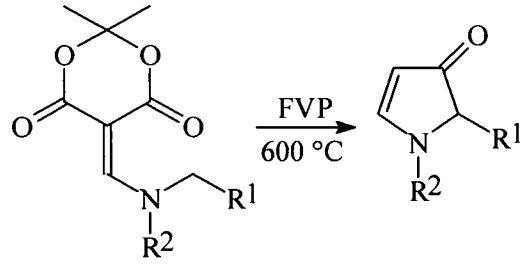
The *O*-alkylated pyridines were also pyrolysed and in the case of the 2-(*p*-chlorophenoxymethoxy)pyridine, the initial heterocycle and *p*-chlorophenol were produced. As before, the 'missing' CH_2 group was detected as ethylene by bromine trapping experiments suggesting that this compound also acts as a carbene generator. The 4-(*p*-chlorophenoxymethoxy)pyridine resulted in rearrangement products which have been rationalised by work by De Mayo.[89]

It should be noted that the pyrolysis reactions of these compounds are influenced by the position of the carbonyl group, *e.g.* the *N*-(4-chlorophenoxymethyl)pyridin-4-one only undergoes a ring expansion reaction and *N*-(4-chlorophenoxymethyl)pyridin-2-one only acts as a carbene generator.

B. ATTEMPTED SYNTHESIS OF AZEPINONES AND THIEPINONES.

3.1 Preamble.

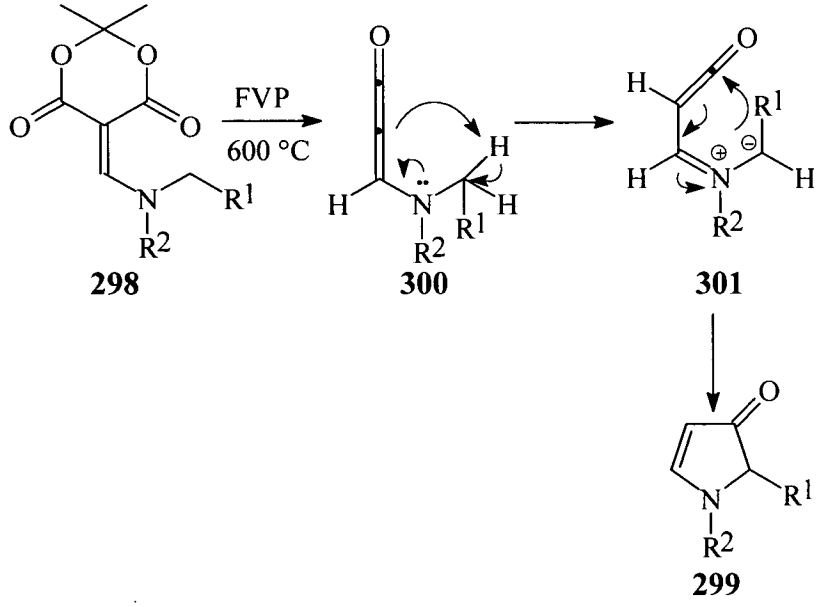
McNab and co-workers[91, 92] have used flash vacuum pyrolysis reactions in the synthesis of 1*H*-pyrrol-3(2*H*)-ones. The general reaction is shown in **Scheme 111**. When Meldrum's acid derivatives **298** were pyrolysed at 600 °C, it resulted in the pyrrolones **299** in ~70% yield.



298 **299**

Scheme 111

This method has general synthetic applicability, and alkyl and aryl 1,2,2-trisubstituted, 1,2-disubstituted and 1-substituted 1*H*-pyrrol-3(2*H*)-ones **299** have all been successfully prepared *via* the pyrolysis of the appropriately substituted Meldrum's acid precursor. The mechanism for this reaction is shown in **Scheme 112**.

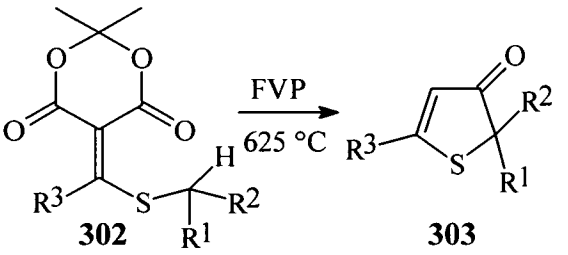


298 **300** **301** **299**

Scheme 112

Compound **298** results in methyleneketene **300** when pyrolysed at 600 °C. This intermediate **300** can undergo a hydrogen shift to dipolar intermediate **301** which can then cyclise to give pyrrolone **299**.

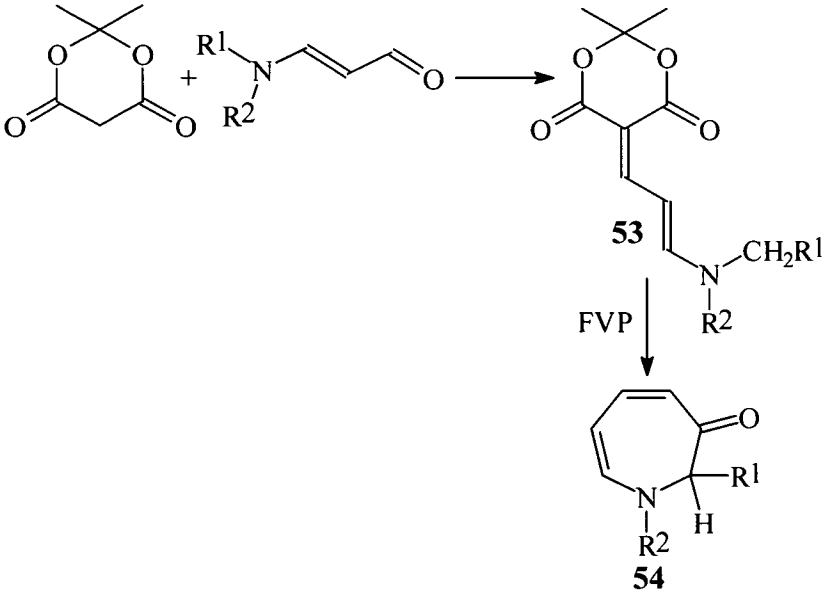
This work was extended by McNab and co-workers[93, 94] to the corresponding sulfur compounds, as shown in **Scheme 113**. Compound **302** results in thiophen-3(2*H*)-one **303** when pyrolysed at 625 °C.



Scheme 113

A range of 2-substituted, 2,2-disubstituted and 5-substituted compounds have all been made *via* this route and the mechanism is analogous to that shown in **Scheme 112**.

McNab and co-workers[18, 19] then investigated the pyrolysis behaviour of compounds **53** which had a second double bond between the heteroatom and the Meldrum's ring. When these precursors were subjected to FVP conditions, they resulted in the seven-membered 1*H*-azepin-3(2*H*)-ones **54**, as shown in **Scheme 114**. It should be noted that this is the only rational synthesis of compounds **54**.



Scheme 114

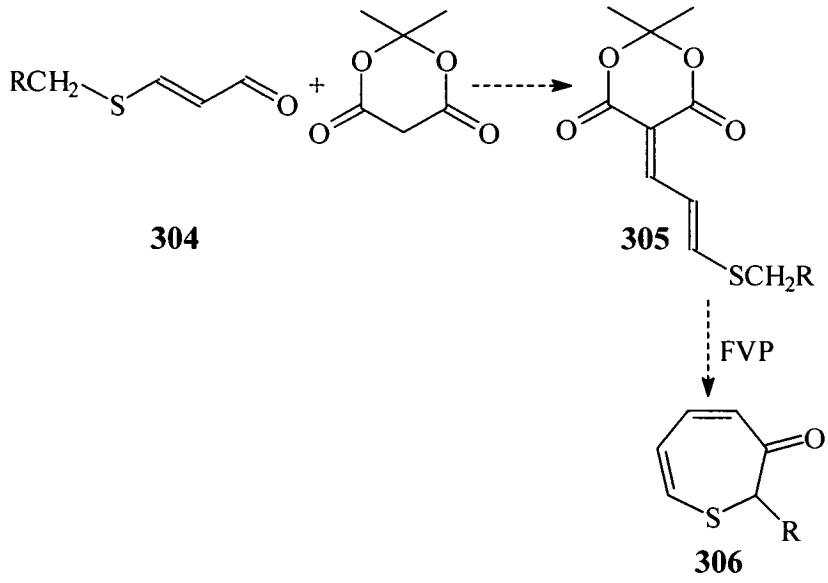
The synthesis of precursors **53** involves the reaction of enaminals,[95] which can be obtained in moderate yields by well established methods, with Meldrum's acid. The flash vacuum pyrolysis of these derivatives results in the azepinone **54** in ~60%

yield. [A more detailed review of this work is contained in the introduction-**Section 1.3.3.**]

3.2 Attempted Synthesis of Thiepinones.

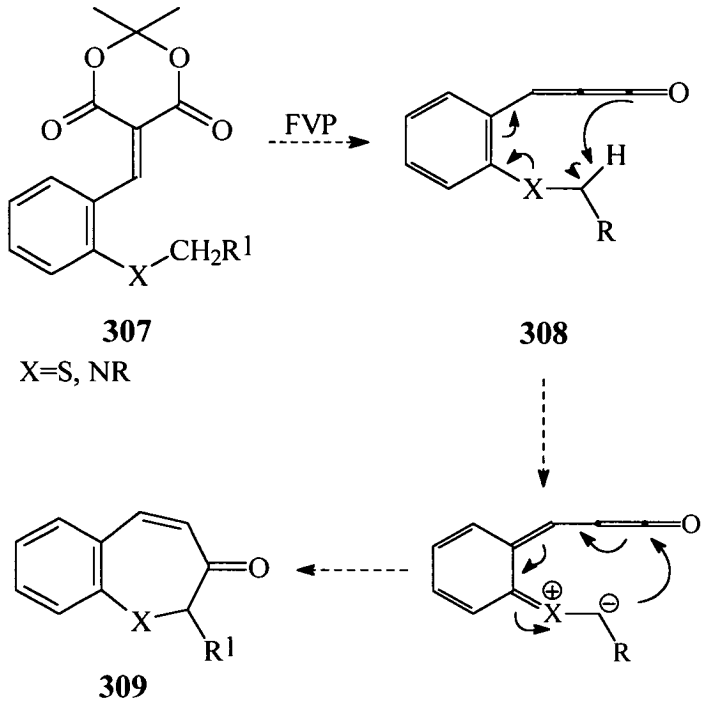
In the following project, it was anticipated that the successful extension of the nitrogen chemistry to the sulfur chemistry in the five-membered series may also be applicable in the seven-membered series.

It was hoped to extend this route to azepinones, to the synthesis of the corresponding unknown sulfur compounds **306**, using an equivalent method, as shown in **Scheme 115**.



Scheme 115

The second part of the work contained in this chapter discusses the replacement of double bond of the Meldrum's acid derivatives as in **307**. This would be an investigation of the reactivity of the methyleneketene intermediate **308**. To get product **309**, the aromaticity of the benzene ring must be disrupted which would be disfavourable. However, this may be overcome if the methyleneketene is very reactive. This could be a potential route to benzazepinones and benzothiepinones.



307 **308**

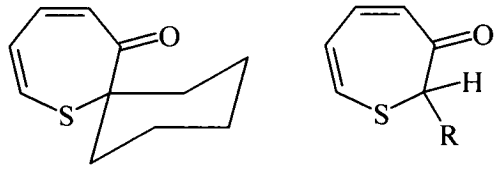
309

Scheme 116

3.2.1 Synthesis of 3-sulfanylpropenals.

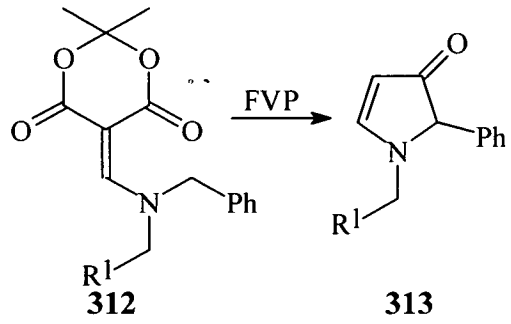
Initially a route to the sulfur analogue **304** of the enaminals was required. Two thiols were initially chosen for investigation and these were cyclohexanethiol and phenylmethanethiol.

The cyclohexanethiol was selected as it is a less volatile thiol, which makes handling it less difficult. It would also produce thiepinone **310** which is 2,2-disubstituted and therefore a relatively reactive C-H would be blocked.



310 **311**

The phenylmethanethiol was selected as the second thiol due to the pyrolysis behaviour of the benzyl group in the pyrrolone synthesis.[92] This is illustrated in **Scheme 117**.

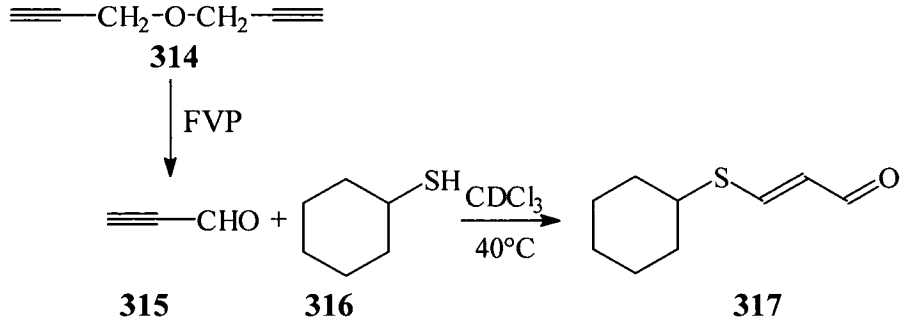


312 **313**

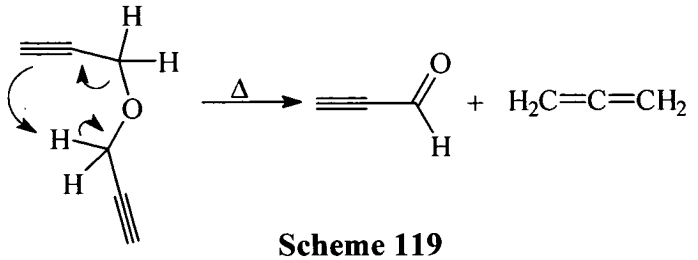
Scheme 117

When compound **312** was pyrolysed, the hydrogen transfer from the benzylic site took place with complete specificity to give a general synthesis of 2-phenylpyrrol-3(2*H*)-ones **313**. These compounds are formed exclusively, regardless of other potentially reactive sites. The authors suggest that this may be due to the phenyl group providing stabilisation at some stage in the hydrogen transfer-cyclisation mechanism. Therefore, it was anticipated that for a proton to transfer in the desired synthesis, it would be most likely to from a benzyl group.

A literature route[96] to the 3-cyclohexylsulfanylpropenal **317** was used which involved reacting propynal **315** and cyclohexanethiol **316** in [^{2}H]chloroform at 40 °C, and compound **317** was obtained in 64% yield. The propynal **315** for this reaction was synthesised in 80% yield by the flash vacuum pyrolysis of diprop-2-ynyl ether **314** *via* a retro-ene mechanism.[97] This is shown in **Scheme 118** with the mechanism for propynal synthesis shown in **Scheme 119**.

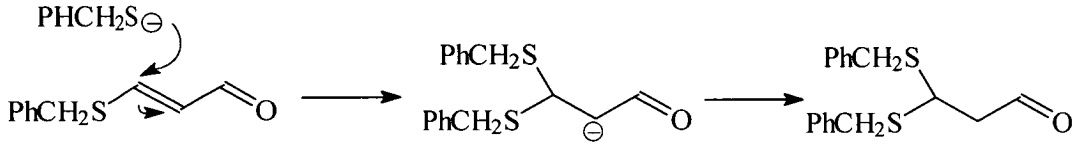


Scheme 118



Scheme 119

However, this method was unsuccessful when applied to the phenylmethanethiol with recovery of only unreacted thiol, so an alternative route was sought. Preliminary work[98] within the group has shown that the reaction of isopropyl thiol with propynal in methanol using triethylamine as a base, yields the appropriate product. However, when this was repeated using phenylmethanethiol, two products were formed. The first was the expected 3-benzylsulfanylpropenal **318** and the second product was identified as compound **319**. This was formed by compound **318** undergoing a second Michael reaction to give compound **319**, as shown in **Scheme 120**.

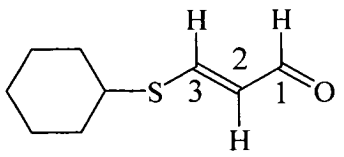


318 **319**

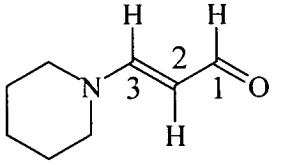
Scheme 120

Attempts to prevent this second Michael reaction, by adding the base and thiol in a dilute solution to excess propynal, had no effect on the product ratio, and it was also found that the base was necessary for the reaction to take place. However, the two obtained products **318** and **319** could be separated by dry flash chromatography in yields of 23% and 20% respectively, with the elution of compound **318** occurring first.

When the NMR data for compound **317** was compared with related enaminal **320**, some interesting differences were identified.[99]



317



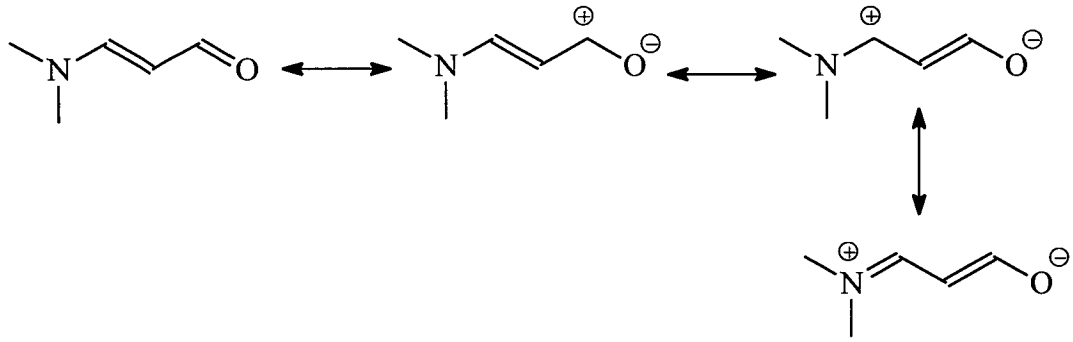
320

The chemical shifts of the protons and carbons at positions 1, 2 and 3 of compounds **317** and **320** are shown in **Table 15.**

Position	δ_H/ppm and *J*/Hz		δ_C/ppm	
	Compound **317**	Compound **320**	Compound **317**	Compound **320**
1	7.57, d, 15.2	6.87, d, 12.6	189.88	189.18
2	6.12, dd, 15.2, 7.6	5.06, dd, 12.6 8.3	125.96	100.17
3	9.32, d, 7.6	8.92, d, 8.3	156.18	159.02

Table 15:- Some proton and carbon chemical shifts of compounds **317** and **320**.

Compound **320** and its resonance structures are shown in **Scheme 121**.



Scheme 121

This suggests that there is a δ+ on two carbons as shown in **Figure 17**.

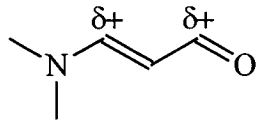
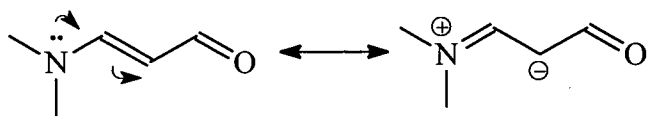


Figure 17

This can also occur with the sulfur compound **317**, which would explain the similarity in the carbon chemical shifts for carbons 1 and 3.

When the delocalisation of the lone pair is considered, it also results in a resonance structure as shown in **Scheme 122**.



Scheme 122

This suggests that there is a δ- on the central carbon as shown in **Figure 18**.

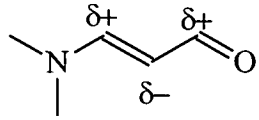
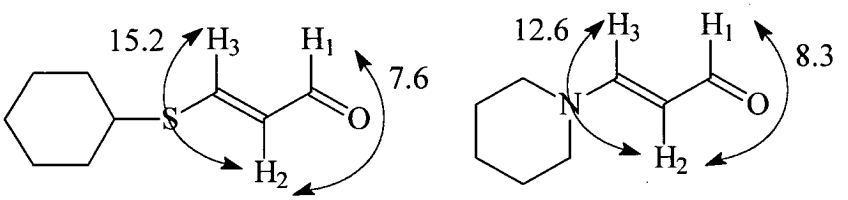


Figure 18

The difference in the chemical shift for the carbon 2 in compounds **320** and **317** respectively, is ~25 ppm which must be attributed to the ability of the heteroatom to donate its lone pair across the conjugated system. This suggests that the nitrogen atom is able to do this more readily than the sulfur, hence compound **320** has a significantly lower chemical shift for carbon 2.

A pattern can also be observed in the proton chemical shifts. In compound **317**, protons 1 and 2 have chemicals shifts that are 0.4 and 0.7 ppm higher than the corresponding protons in compound **320,** and the chemical shift of proton 2 is 1 ppm higher than that in compound **320**. This suggests that donation of the nitrogen lone pair across the conjugated system in compound **317** has a greater effect on the chemical shift of this proton than the corresponding donation of the sulfur lone pair in compound **320**.

There are also significant differences in the coupling constants for these compounds, as shown in **Figure 19**.



317 **320**

Figure 19

The coupling constant between protons H_2 and H_3 in compound **317** is 15.2 Hz and in compound **320**, this is significantly smaller at 12.6 Hz. It is also noted that the coupling constant between H_1 and H_2 is smaller in compound **317** than in compound **320**. This suggests that compound **317** exists as in **Figure 19** with distinct single and double bonds which is dictated by the values of the coupling constants. In compound **320**, the two coupling constants are closer in value suggesting that the single and double bonds are more equivalent, as shown in **Figure 20**.

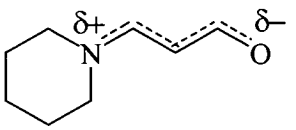
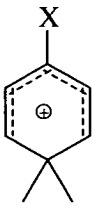


Figure 20

The σ^+ values for the substituents in compounds **321a** and **321b** are shown in **Figure 21**.[100]



321

a; X=SMe; σ^+ =–0.6
b; X=NMe_2; σ^+ =–1.7

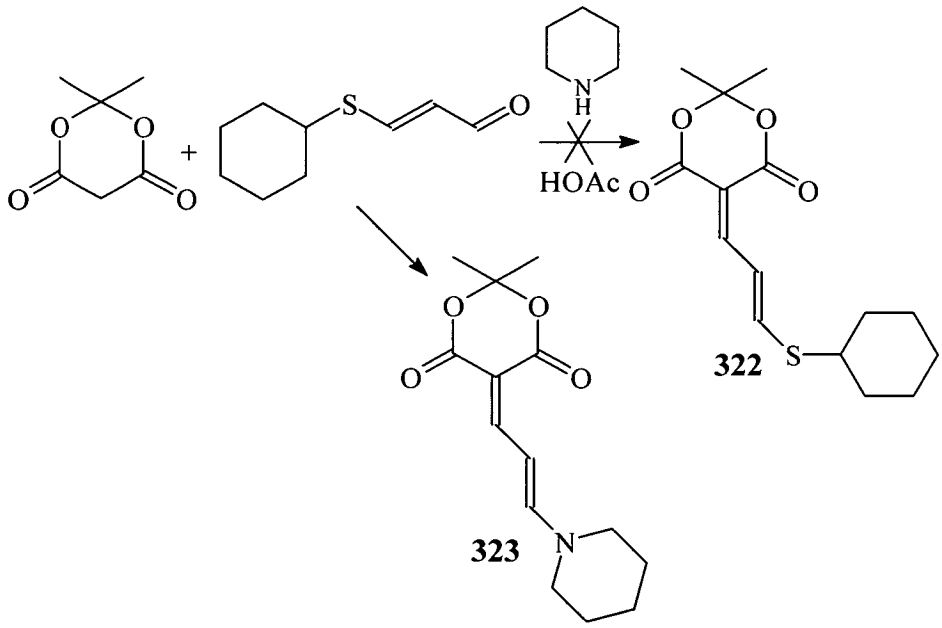
Figure 21

The σ^+ value measures the extent to which an electron-donating group X interacts with the developing positive charge of the transition state in an electrophilic aromatic substitution reaction. The negative sign indicates that the groups are electron donating, and it can be seen that there is an order of magnitude difference between the nitrogen group value of -1.7 and the sulfur group value of -0.6. This supports the observation that the nitrogen atom can donate its lone pair to a greater extent in compound **320** than sulfur can in compound **317**.

3.2.2 Reaction of 3-sulfanylpropenals with Meldrum's acid.

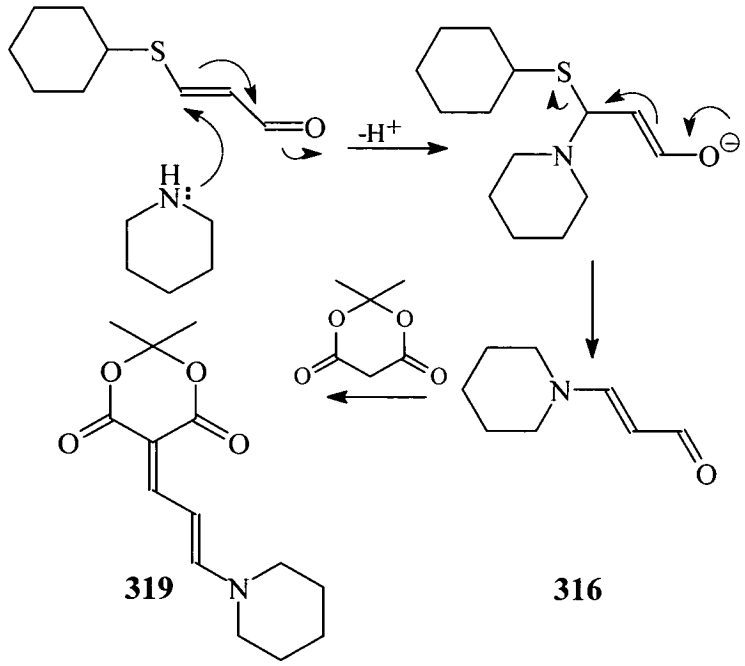
McNab and co-workers[101, 102] have collated three methods for the condensation of Meldrum's acid with carbonyl compounds. The first method involves stirring an equimolar amount of Meldrum's acid with the carbonyl compound in toluene with catalytic amounts of piperidine and acetic acid and has been found to work well for aldehydes. The second method involves stirring equimolar amounts of Meldrum's acid and the carbonyl compound in pyridine and works for ketones. It should be noted that this was the method of choice for the reaction of enaminals with Meldrum's acid with the enaminals proving to be inert under the conditions of the first method. The third method involves the addition of the Meldrum's acid and carbonyl compound to a solution of titanium tetrachloride in carbon tetrachloride in THF, followed by the addition of a solution of pyridine in THF and has been found to work well for ketones.[103]

Initially the first method was used for the condensation of 3-cyclohexylsulfanylpropenal **317** with Meldrum's acid. However, there was no evidence of desired product compound **322**, but compound **323** was isolated by dry flash chromatography in 7% yield, and was identified by comparison with literature spectra.[99] This is outlined in **Scheme 123**.



Scheme 123

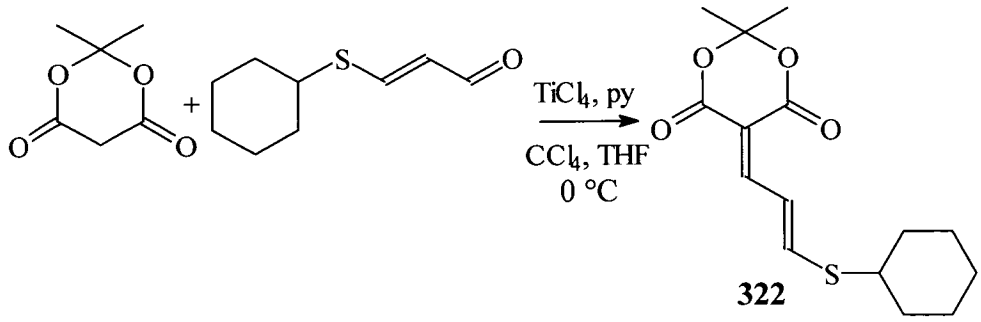
This suggests that the piperidine catalyst displaces the sulfur group from sulfanyl-propenal **317**, and then enaminal **320** reacts with the Meldrum's acid to give compound **323**, as shown in **Scheme 124**.



Scheme 124

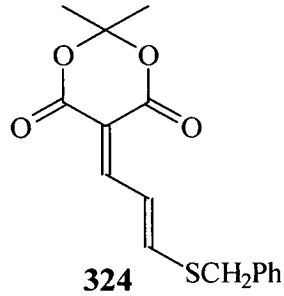
When the second condensation method was used, no identifiable products were obtained.

When the third condensation method was used, it resulted in compound **322** in 36% yield after chromatography, as shown in **Scheme 125**.



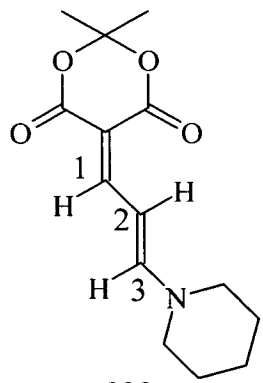
Scheme 125

The same method was used for the synthesis of compound **324** and this was obtained in 32% yield.

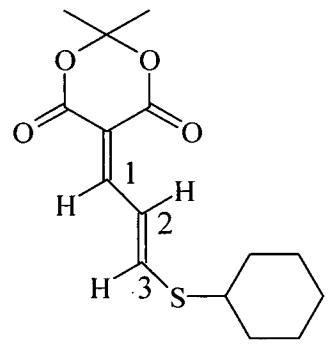


324

When the NMR data for compound **323** and **322** was compared, some interesting differences were identified. The chemical shifts for carbons 1, 2 and 3 are shown in **Table 16**.



323



322

Compound **323** δ_C/ppm	Compound **322** δ_C/ppm
161.24	160.11
158.62	156.02
101.75	122.37

Table 16:- Some carbon chemical shifts of compounds **323** and **322**.

This information indicates that there is ~2 ppm difference in the chemical shift between the compounds except for one signal which must be the carbon 2. In compound **323**, this carbon appears at 101.75 ppm and in compound **322**, at 122.37 ppm. This large difference must be due to the nature of the heteroatom, and can be rationalised in a similar manner to compounds **317** and **320**. However, it should be noted that the difference in the chemical shift of carbon 2 in compounds **323** and **322** matches almost exactly the difference in the chemical shift of carbon 2 in compounds **317** and **320**. This suggests that the heteroatoms have equivalent electron donating ability in the both sets of compounds.

In the proton spectrum of compound **323**, the protons, H_1, H_2 and H_3 are all distinct and occur in the chemical shift range of 6.73 - 7.98 ppm. In compound **322**, they occur in a multiplet over a smaller range of 7.71 - 7.95 ppm and therefore a direct comparison cannot be made. However, it is noted that compound **322** has higher chemical shifts of ~1 ppm which again almost matches the difference in the chemical shifts of compounds **317** and **320**.

The structures of compounds **322** and **324** were further confirmed by X-ray crystallography. The structures of compounds **322** and **324** are shown in **Figures 22** and **23** with the corresponding data in **Tables 17, 18, 19** and **20**.

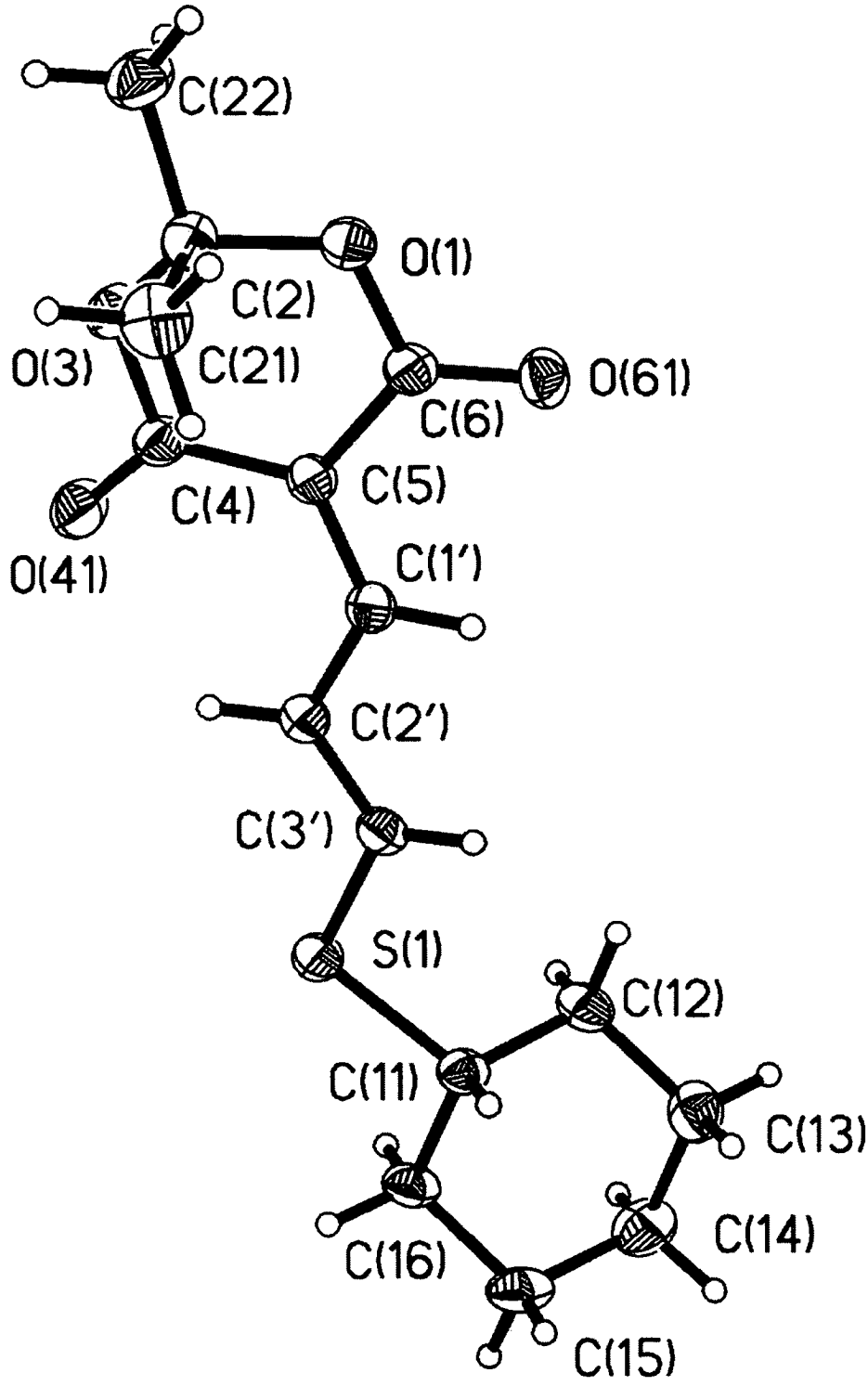

C(22)
O(1)
C(2)
O(3)
C(21)
O(61)
C(6)
C(4)
C(5)
O(41)
C(1')
C(2')
C(3')
S(1)
C(12)
C(11)
C(13)
C(14)
C(16)
C(15)

Figure 22

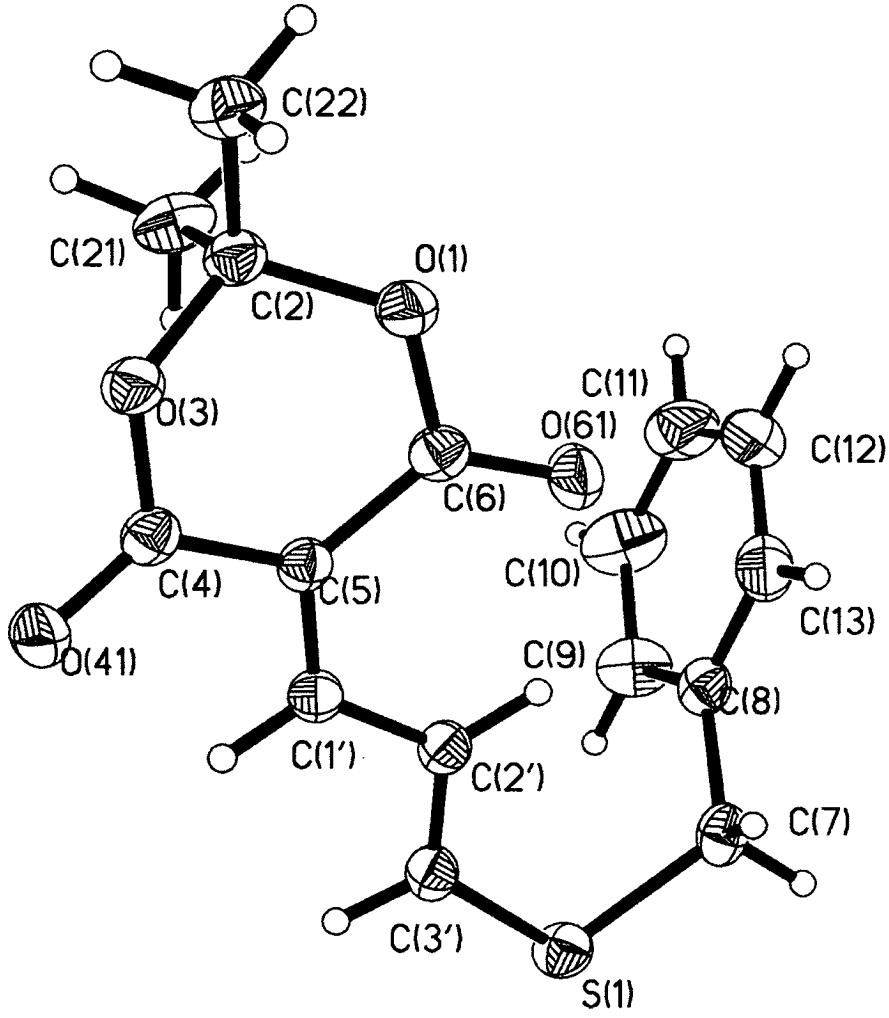

C(22)
C(21)
O(1)
C(2)
O(3)
C(11)
O(61)
C(12)
C(6)
C(4)
C(5)
C(10)
C(13)
O(41)
C(9)
C(8)
C(1')
C(2')
C(7)
C(3')
S(1)

Figure 23

Table 17 Bond Lengths (Å)

O(1) - C(6)	1.350 (2)
O(1) - C(2)	1.438 (2)
C(2) - O(3)	1.442 (2)
C(2) - C(22)	1.506 (3)
C(2) - C(21)	1.508 (3)
O(3) - C(4)	1.364 (2)
C(4) - O(41)	1.206 (2)
C(4) - C(5)	1.463 (2)
C(5) - C(2')	1.366 (2)
C(5) - C(6)	1.471 (2)
C(6) - O(61)	1.209 (2)
C(1') - C(2')	1.418 (2)
C(2') - C(3')	1.355 (2)
C(3') - S(1)	1.7088 (17)
S(1) - C(11)	1.8251 (18)
C(11) - C(12)	1.522 (2)
C(11) - C(16)	1.522 (2)
C(12) - C(13)	1.527 (3)
C(13) - C(14)	1.528 (3)
C(14) - C(15)	1.522 (3)
C(15) - C(16)	1.529 (3)

Table 18 Bond Angles (degrees)

C(6) - O(1) - C(2)	118.69 (13)
O(1) - C(2) - O(3)	109.82 (13)
O(1) - C(2) - C(22)	106.56 (15)
O(3) - C(2) - C(22)	105.76 (14)
O(1) - C(2) - C(21)	109.99 (15)
O(3) - C(2) - C(21)	110.68 (15)
C(22) - C(2) - C(21)	113.85 (16)
C(4) - O(3) - C(2)	118.70 (13)
O(41) - C(4) - O(3)	117.85 (15)
O(41) - C(4) - C(5)	126.37 (16)
O(3) - C(4) - C(5)	115.71 (14)
C(1') - C(5) - C(4)	123.22 (15)
C(1') - C(5) - C(6)	117.72 (15)
C(4) - C(5) - C(6)	118.82 (14)
O(61) - C(6) - O(1)	118.43 (14)
O(61) – C(6) – C(5)	124.31 (15)
C(5) – C(1') – C(2')	128.48 (16)
C(3) – C(2') – C(1')	119.33 (16)
C(2') – C(3') – S(1)	123.18 (14)
C(3') – S(1) – C(11)	102.90 (8)
C(12) – C(11) – C(16)	110.94 (14)
C(12) – C(11) – S(1)	113.94 (12)
C(16) – C(11) – S(1)	106.03 (12)
C(11) – C(12) – C(13)	109.13 (15)
C(12) – C(13) – C(14)	111.77 (17)
C(15) – C(14) – C(13)	111.30 (16)
C(14) – C(15) – C(16)	111.42 (16)
C(11) – C(16) – C(15)	110.40 (15)
O(1) – C(6) – C(5)	117.19 (14)

Table 19 Bond Lengths (Å)

S(1) - C(3')	1.7074 (15)
S(1) - C(7)	1.8047 (15)
O(3) - C(4)	1.3631 (17
O(3) - C(2)	1.4392 (16)
O(1) - C(6)	1.3597 (17)
O(1) - C(2)	1.4334 (17)
O(41) - C(4)	1.2026 (16)
O(61) - C(6)	1.2046 (17)
C(5) - C(1')	1.3589 (19)
C(5) - C(6)	1.4662 (19)
C(5) - C(4)	1.4712 (19)
C(2') - C(3')	1.348 (2)
C(2') - C(1')	1.4167 (19)
C(7) - C(8)	1.509 (2)
C(2) - C(22)	1.501 (2)

Table 20 Bond Angles (degrees)

C(3') - S(1) - C(7)	104.31 (7)
C(4) - O(3) - C(2)	117.60 (10)
C(6) - O(1) - C(2)	118.46 (11)
C(1') - C(5) - C(6)	122.95 (13)
C(1') - C(5) - C(4)	118.47 (13)
O(41) - C(4) - O(3)	118.02 (13)
O(41) - C(4) - C(5)	125.43 (13)
O(3) - C(4) - C(5)	116.45 (12)
C(3') - C(2') - C(1')	120.36 (13)
O(61) - C(6) - O(1)	117.45 (13)
O(61) - C(6) - C(5)	126.02 (13)
O(1) - C(6) - C(5)	116.48 (12)
C(5) - C(1') - C(2')	128.17 (13)
C(8) - C(7) - S(1)	116.08 (10)
C(6) - C(5) - C(4)	118.40 (12)

C(2) - C(21)	1.510 (2)	O(1) - C(2) - O(3)	109.71 (11)
C(8) - C(13)	1.383 (2)	O(1) - C(2) - C(22)	105.92 (12)
C(8) - C(9)	1.387 (2)	O(3) - C(2) - C(22)	106.66 (11)
C(9) - C(10)	1.382 (2)	O(1) - C(2) - C(21)	110.65 (12)
C(13) - C(12)	1.385 (2)	O(3) - C(2) - C(21)	109.81 (12)
C(12) - C(11)	1.373 (3)	C(22) - C(2) - C(21)	113.92 (12)
		C(2') - C(3') - S(1)	128.33 (12)
		C(13) - C(8) - C(9)	118.16 (15)
		C(13) - C(8) - C(7)	119.63 (14)
		C(9) - C(8) - C(7)	122.21(14)
		C(10) - C(9) - C(8)	120.68(17)
		C(8) - C(13) - C(12)	120.81(16)
		C(11) - C(12) - C(13)	120.40 (17)
		C(11) - C(10) - C(9)	120.64(18)
		C(10) - C(11) - C(12)	119.28 (16)

Figure 24 shows compounds **322** and **324** with 5-dimethylaminomethylene- and 5-dimethylaminopropenylidene- Meldrum's acid derivatives (**325** and **326** respectively), with some of their bond lengths shown.[104]

In compounds **325**, **322** and **324**, the formal C-C single bonds are consistently longer than those of the formal C=C double bonds as would be expected. However, in compound **326** the opposite is true.

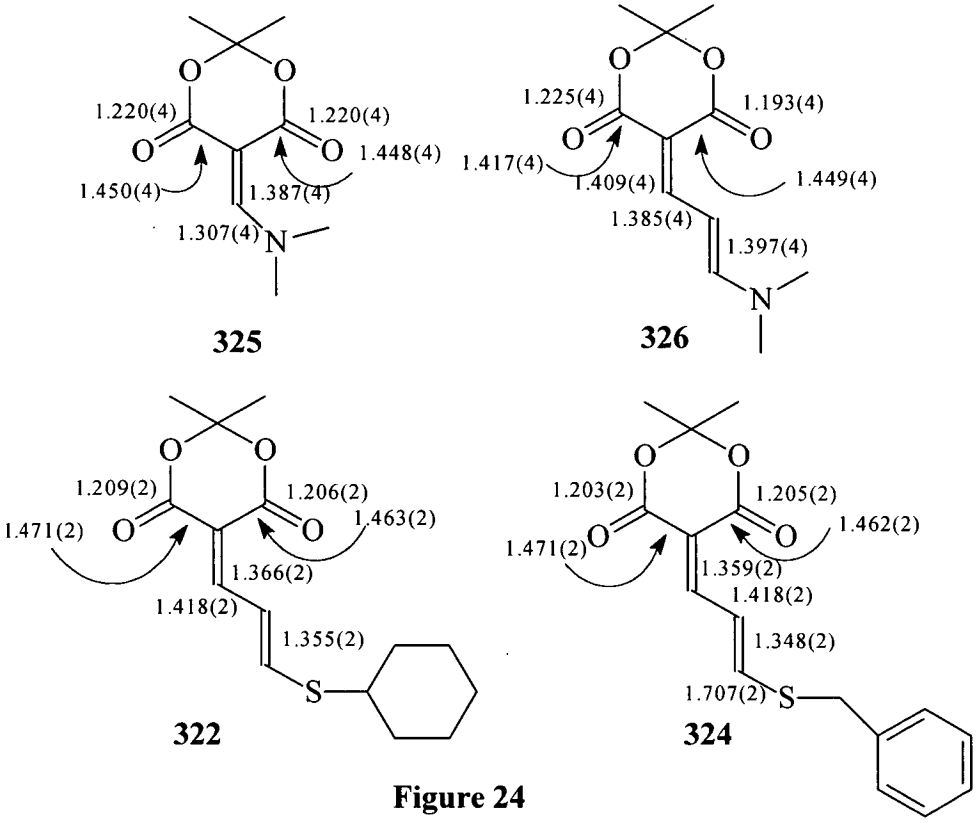
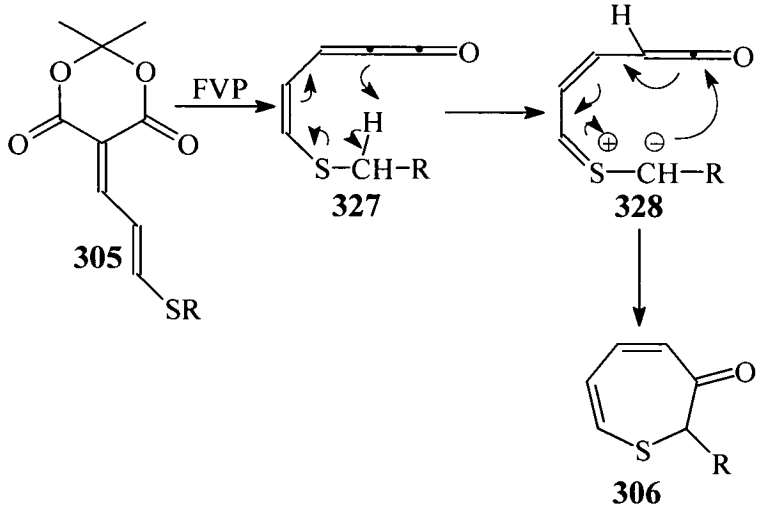


Figure 24

In compound **325**, the bond lengths of the Meldrum's ring are highly symmetrical about the C(2) - C(5) plane but compound **326** shows some evidence of preferred delocalisation to the carbonyl group which is *trans* to the conjugated chain. There is no evidence of this occurring in compound **325**. In compounds **322** and **324**, the C(4) - C(5) and C(5) - C(6) bonds have more single bond character than the corresponding bonds in compound **326**. This suggests that in compound **326**, the nitrogen lone pair has delocalised through the conjugated chain and has a large effect on the bond lengths. This is not observed in compounds **325**, **322** and **324**. It should be noted that the benzyl group curls around unexpectedly in compound **320**, and this has not been observed in these structures before.

3.2.3 Pyrolyses of the Meldrum's acid derivatives.

Compounds **322** and **324** were then subjected to flash vacuum pyrolysis. It was hoped that the Meldrum's acid derivative **305** would lose acetone and carbon dioxide to give the methyleneketene **327**. A hydrogen shift would give the dipolar intermediate **328**, and cyclisation would result in the thiepinone **306**, as shown in **Scheme 126**.

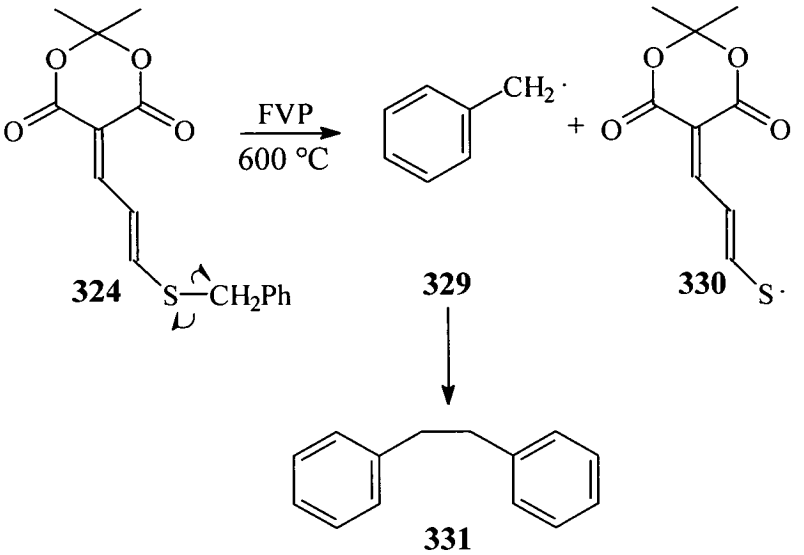


Scheme 126

When compound **322** was pyrolysed at 600 °C, ^{1}H NMR spectroscopy showed no identifiable products. However, although this was a disappointing result, the pyrolysis of other Meldrum's acid derivatives have produced similar results where no products could be identified in the pyrolysate.[105]

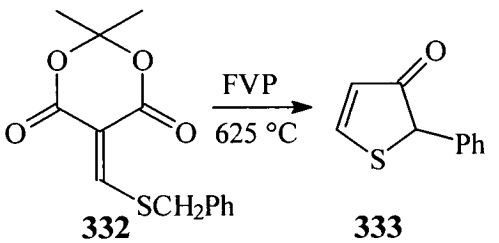
Compound **324** was then subjected to similar pyrolysis conditions, as it was anticipated that the hydrogen shift step of the mechanism would be most likely to

occur for this derivative. In the event, bibenzyl **331** was the only identifiable product in the pyrolysate. This product arose from the radical cleavage of derivative **324** to give radicals **329** and **330**, as shown in **Scheme 127**.



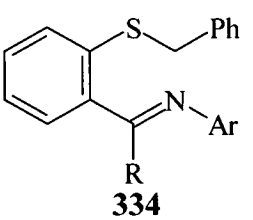
Scheme 127

The benzyl radical **329** is a primary radical which has extra stabilisation due to the attached phenyl group, and dimerisation of this radical produces bibenzyl **331**. This was an unexpected result, as the S-benzyl cleavage is not usually observed at 600 °C. The pyrolysis of compound **332** at 625 °C results in compound **333** in 90% yield with no trace of benzyl cleavage, as shown in **Scheme 128**.[94]



Scheme 128

However, the pyrolysis of compound **334** at the higher pyrolysis temperature of 650 °C showed evidence of benzyl cleavage.[106]

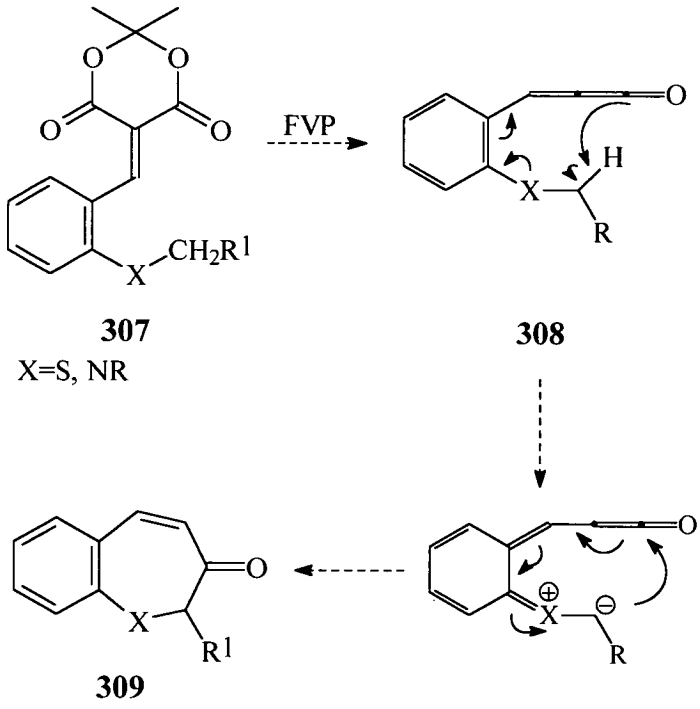


This suggests that in the pyrolysis of compound **324**, the radicals **329** and **330** must have extra stabilisation which causes cleavage of the S-benzyl bond at this lower temperature of 600 °C.

The major difference in the Meldrum's acid precursors **53** and **305** is the electron donation through the conjugated chain to the Meldrum's ring. In compound **53**, the lone pair of the nitrogen atom can be donated through the chain and has a large effect on the bonds lengths of the molecule, as shown in **Figure 24**. This delocalisation must be necessary for the cyclisation to seven-membered compounds **55**. This delocalisation does not occur in the Meldrum's acid precursors **305** and these cyclisation reaction did not work.

3.3 Attempted Synthesis of Benzothiepinones and Benzazepinones.

This work was then extended to investigate the potential synthesis of the corresponding benzazepinones and benzothiepinones. The general method is shown in **Scheme 116**. As the method shown in **Scheme 114** was successful for the synthesis of azepinones, it was hoped that this route could be used for the synthesis of the corresponding benzazepinones. The benzothiepinone systems were investigated to complete the series.



307 X=S, NR

308

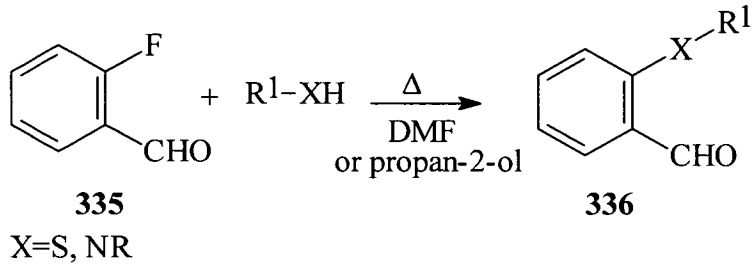
309

Scheme 116

It was anticipated that compounds **307** could be synthesised from the reaction of Meldrum's acid with an *ortho*-substituted benzaldehyde **336**.

3.3.1 Synthesis of *ortho*-Substituted Benzaldehydes.

These aldehydes were synthesised from *o*-fluorobenzaldehyde **335** and the appropriate amine or thiol, as shown in **Scheme 129**. It should be noted that DMF was used as a solvent for the amine reactions, and propan-2-ol for thiol reactions.



335
X=S, NR

336

Scheme 129

This was based on work by Suschitzky *et al*,[107] where the activated fluorine atom of the *o*-fluorobenzaldehyde undergoes a nucleophilic substitution reaction with the appropriate derivative to produce the desired product.

The thiols and amines used are shown in **Table 21** with the yield of compound **336** obtained.

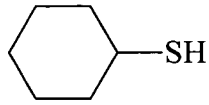
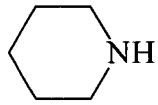
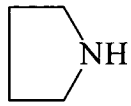
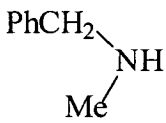
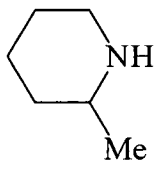
Amine/Thiol used	Yield of compound **336**
$PhCH_2SH$	67%; **a**
	49%, **b**
	78%; **c**
	64%; **d**
	61%; **e**
	48%; **f**

Table 21:- Amines and thiols used in the synthesis of compound **336**.

When this reaction was carried out using methylaniline, diisopropylamine and dibenzylamine as the nucleophile, they all failed to give the desired product with recovery of unreacted starting materials. The unsuccessful nature of these reactions was attributed to the increased steric bulk at the potential reaction site.

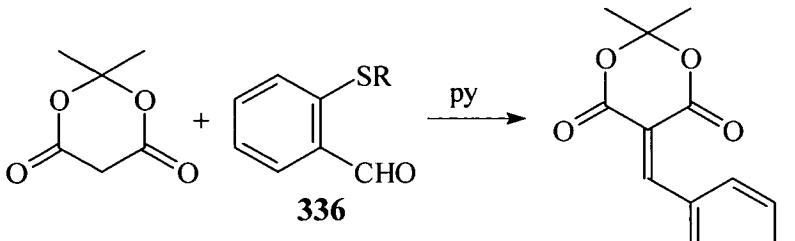
3.3.2 Reaction of *ortho*-substituted benzaldehydes with Meldrum's acid.

In this section, compounds **336a** and **336b** and their subsequent reactions are discussed separately to the benzaldehydes **336c**, **336d**, **336e** and **336f** due to their different reaction pathways.

3.3.2.1 Sulfur compounds

Compounds **336a** and **336b** were stirred overnight in pyridine, and the desired condensation products were produced in moderate yield, as shown in

Scheme 130. It was found that the milder method of stirring overnight in toluene with glacial acetic acid and piperidine did not produce the desired condensation products.



336

a; R=CH_2Ph
b; R=cyclohexyl

337

Scheme 130

A crystal structure of compound **337b** was obtained. This is shown in **Figures 25** and **26**. The associated data is contained in **Tables 22** and **23**. It was obtained to compare with the crystal structures of other Meldrum's derivatives.

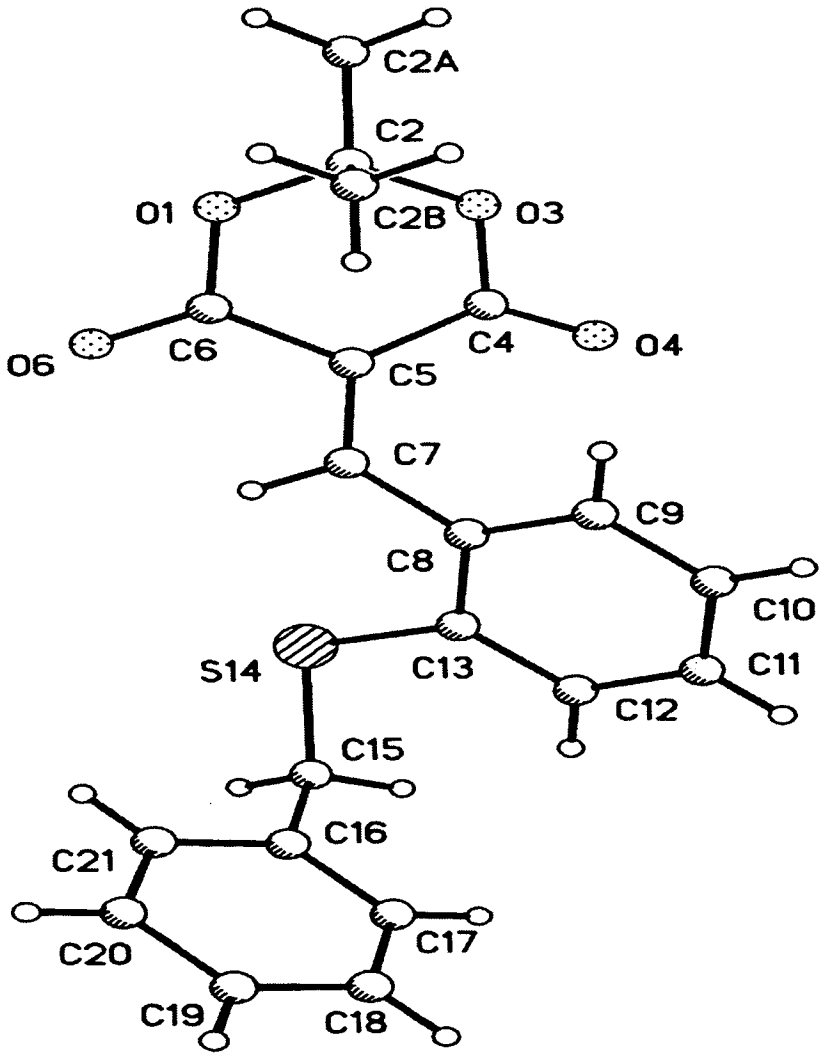


Figure 25

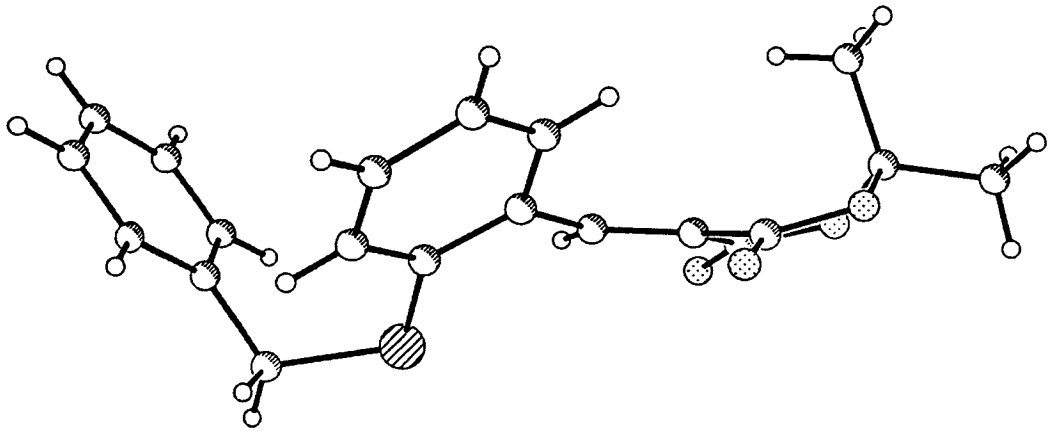


Figure 26

Table 22 Bond Lengths (Å)

O(1) – C(6)	1.3509(19)
O(1) – C(2)	1.446(2)
C(2) – C(3)	1.442(2)
C(2) – C(2B)	1.503(3)
C(2) – C(2A)	1.505(2)
O(3) – C(4)	1.3494(18)
O(4) – C(4)	1.1988(18)
C(4) – C(5)	1.487(2)
C(5) – C(7)	1.342(2)
C(5) – C(6)	1.483(2)
O(6) – C(6)	1.1991(19)
C(7) – C(8)	1.456(2)
C(8) – C(9)	1.399(2)
C(8) – C(13)	1.409(2)
C(9) – C(10)	1.373(2)
C(10) – C(11)	1.382(2)
C(11) – C(12)	1.376(2)
C(12) – C(13)	1.392(2)
C(13) – S(14)	1.7685(15)
S(14) – C(15)	1.8181(15)
C(15) – C(16)	1.507(2)
C(16) – C(17)	1.380(2)
C(16) – C(21)	1.389(2)
C(17) – C(18)	1.385(2)
C(18) – C(19)	1.374(3)
C(19) – C(20)	1.378(2)
C(20) – C(21)	1.380(2)

Table 23 Bond Angles (degrees)

C(6) – O(1) – C(2)	118.53(13)
O(3) – C(2) – O(1)	109.29(13)
O(3) – C(2) – C(2B)	110.76(15)
O(1) – C(2) – C(2B)	110.73(15)
O(3) – C(2) – C(2A)	105.65(16)
O(1) – C(2) – C(2A)	105.45(15)
C(2B) – C(2) – C(2A)	114.66(17)
C(4) – O(3) – C(2)	119.68(12)
O(4) – C(4) – O(3)	118.69(14)
O(4) – C(4) – C(5)	125.39(14)
O(3) – C(4) – C(5)	115.80(13)
C(7) – C(5) – C(6)	117.66(14)
C(7) – C(5) – C(4)	125.40(14)
C(6) – C(5) – C(4)	116.75(13)
O(6) – C(6) – O(1)	118.79(15)
O(6) – C(6) – C(5)	125.45(15)
O(1) – C(6) – C(5)	115.71(13)
C(5) – C(7) – C(8)	129.35(14)
C(9) – C(8) – C(13)	118.31(14)
C(9) – C(8) – C(7)	121.34(14)
C(13) – C(8) – C(7)	120.34(13)
C(10) – C(9) – C(8)	121.67(15)
C(9) – C(10) – C(11)	119.23(15)
C(12) – C(11) – C(10)	120.78(16)
C(11) – C(12) – C(13)	120.49(15)
C(12) – C(13) – C(8)	119.37(13)
C(12) – C(13) – S(14)	122.70(11)
C(8) – C(13) – S(14)	117.73(11)

C(13) – S(14) – C(15)	103.95(7)
C(16) – C(15) – S(14)	115.22(10)
C(17) – C(16) – C(21)	118.61(14)
C(17) – C(16) – C(15)	121.24(14)
C(21) – C(16) – C(15)	120.13(14)
C(16) – C(17) – C(18)	120.64(15)
C(19) – C(18) – C(17)	120.22(16)
C(18) – C(19) – C(20)	119.72(16)
C(19) – C(20) – C(21)	120.11(16)
C(20) – C(21) – C(16)	120.69(15)

Figure 27 shows compounds **326, 324** and **337b** with some of their bond lengths shown.

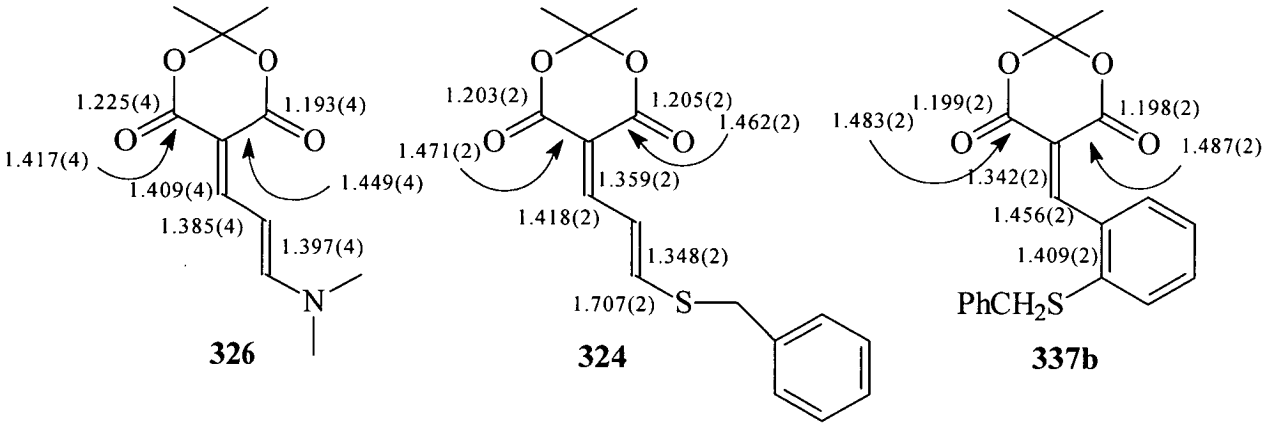


Figure 27

Compound **337b** has longer bonds in the Meldrum's ring than both compounds **326** and **324**. The formal double bond in compound **337b** is shorter than the corresponding bonds in compounds **326** and **324**, and the formal single bonds are longer than those in **324** and **326**. This suggests that the presence of the benzene ring in compound **337b** blocks the delocalisation of the sulfur lone pair. In compound **324**, there is slight delocalisation of the sulfur lone pair, but in compound **326** the nitrogen lone pair can delocalise through the conjugated chain and has a huge effect on bond lengths. In compound **326**, the C(4) - C(5) and C(5) - C(6) single bonds show some double bond character which is illustrated by their shorter length and may be attributed to the delocalisation of the nitrogen lone pair through the conjugated portion of this molecule. In compound **324** these bonds are longer, and in compound **337b** they are longer again, indicating that these bonds have more single bond character in these compounds. This suggests that there is a slight delocalisation of the sulfur lone pair across the conjugated portion of compound **324**, but this delocalisation is blocked by the benzene ring in compound **337b**.

It should be noted that the unexpected "tail-curl" that is observed in the structure of compound **324** is not observed in compound **337b**. This must be due to the presence of the benzene ring.

3.3.2.2 Pyrolysis of sulfur compounds.

The pyrolysis of compounds **337a** and **337b** did not produce the desired benzothiepinones, however this is not entirely surprising considering the unsuccessful nature of the pyrolysis of compounds **322** and **324**.

When compound **337b** was subjected to FVP conditions at 525 °C, bibenzyl again was the only identifiable product in the pyrolysate. This was formed in a similar manner as in **Scheme 127**. Pyrolysis at lower temperatures resulted in the recovery of unreacted starting materials. This was again a surprising result with the S-benzyl cleavage occurring at a lower temperature than has been previously observed. (see **Section 3.2.3**) This implies that the radicals formed initially during the pyrolysis reaction have extra stabilisation.

When compound **337a** was pyrolysed at 600 °C, ^{1}H NMR spectroscopy showed no identifiable products, and again starting material was recovered from pyrolysis reactions at lower temperatures. However, although this was a disappointing result, the pyrolysis of other Meldrum's acid derivatives have produced similar results where no products could be identified in the pyrolysate.[105]

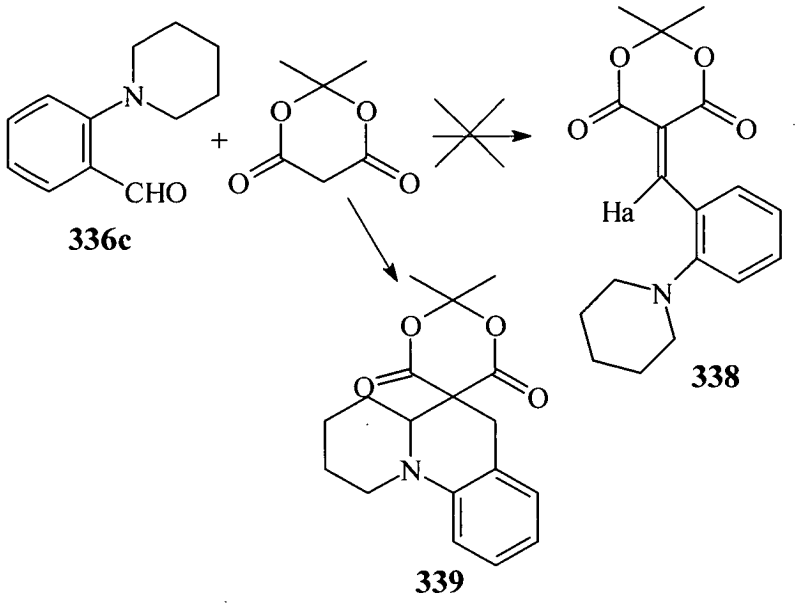
As before, the unsuccessful nature of these pyrolysis reactions was attributed to the lack of electron donation through the conjugated system

3.3.2.3 Nitrogen Compounds.

Compounds **336c**, **336d**, **336e** and **336f** were reacted with Meldrum's acid using the standard conditions of either stirring overnight in pyridine, or the milder conditions of stirring overnight in toluene with piperidine and acetic acid.

It was anticipated that the Knoevenagel condensation reaction between Meldrum's acid and compound **336c** would proceed to yield compound **338**. However, the absence of the characteristic signal for H_a at 8 – 9 ppm on the ^{1}H NMR spectrum suggested that this was not happening, and that an alternative reaction was occurring. The ^{13}C NMR spectrum was also unusual as it contained five CH_2 signals in different environments which would not occur in the carbon spectrum of **338**. However, the molecular ion peak on the mass spectrum occurred at the expected *m/z* value of 315,

suggesting that the product was isomeric with **338**. This information allowed structure **339** to be proposed, and this was confirmed by a crystal structure. Compound **339** was obtained in 54% yield, as shown in **Scheme 131**.



Scheme 131

This structure was confirmed by a crystal structure which is shown in **Figure 28**. The associated data for this structure is contained in **Tables 24** and **25**. This structure clearly demonstrates the cyclised nature of compound **339**. The resulting rigidity causes the two methyl groups of Meldrum's acid to be in two slightly different environments. This accounts for the two different methyl peaks in the ^{1}H NMR spectrum. When structure **339** is compared with that of compound **337b**, the C(4) – C(5) and C(5) – C(6) of the Meldrum's ring in compound **339** are longer than in compound **337b** indicating that they have more single bond character. This may be due to compound **337b** having a double bond at the 5-position and compound **339** having 2 single bonds at this position. This reaction can be rationalised in terms of the "tertiary amino effect." This is a term that has been employed by Meth-Cohn and Suschitzky[108] to generalise the cyclisation reactions that certain *ortho*-substituted *N,N*-dialkylanilines undergo. The majority of work on the tertiary amino effect with respect to a vinyl moiety has been carried out by Reinhoudt and Verbroom,[109] and is well reported in the literature.

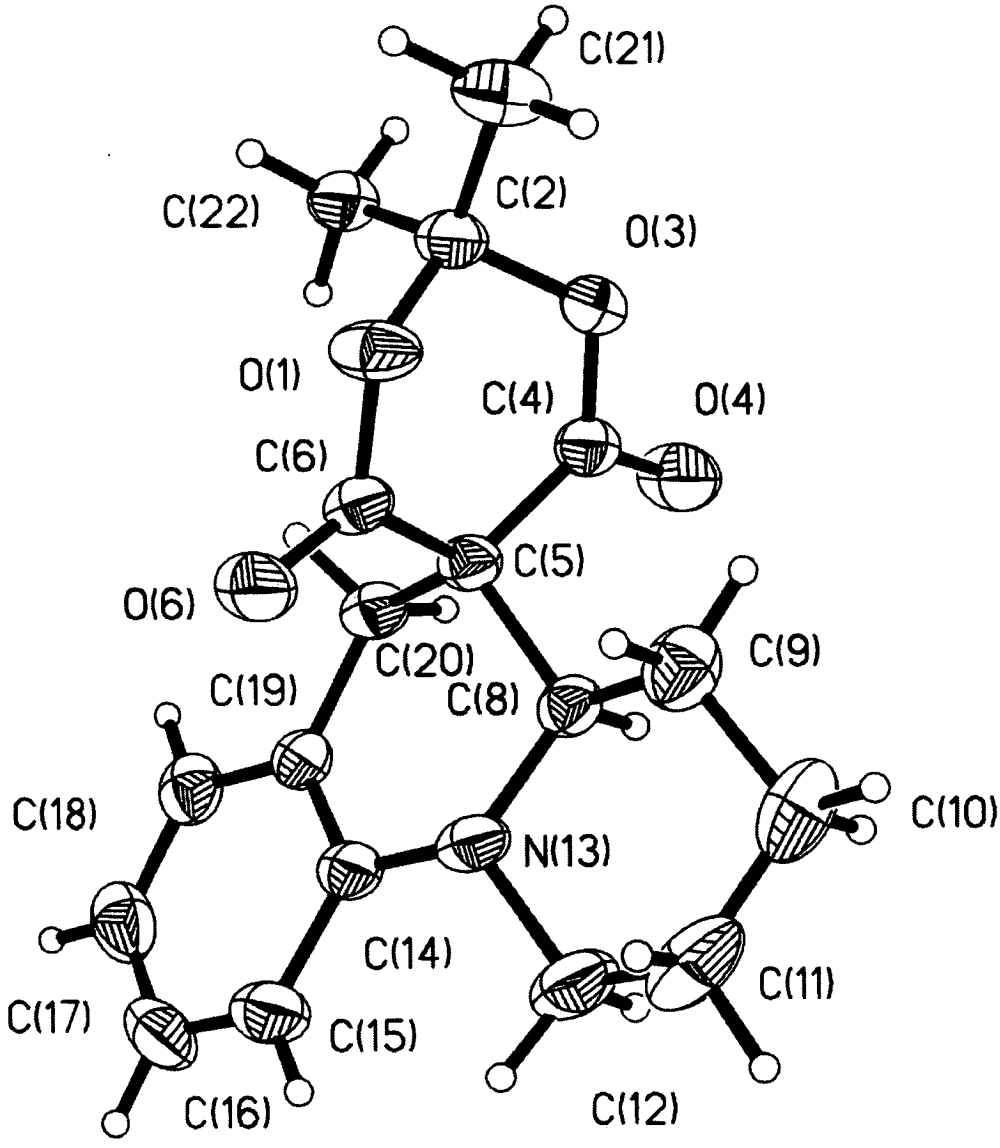

C(21)
C(22)
C(2)
O(3)
O(1)
C(4)
O(4)
C(6)
C(5)
O(6)
C(20)
C(9)
C(19)
C(8)
C(18)
C(10)
N(13)
C(14)
C(11)
C(17)
C(15)
C(16)
C(12)

Figure 28

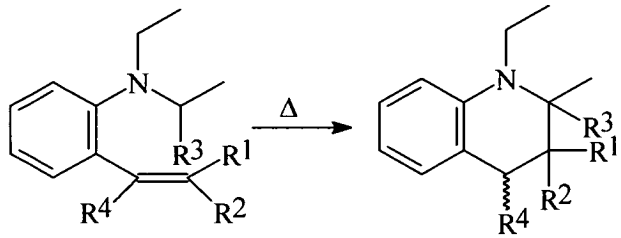
Table 24 Bond Lengths (Å)

O(1) – C(6)	1.356(2)
O(1) – C(2)	1.436(2)
C(2) – O(3)	1.436(2)
C(2) – C(22)	1.495(3)
C(2) – C(21)	1.507(3)
O(3) – C(4)	1.346(2)
C(4) – O(4)	1.201(2)
C(4) – C(5)	1.521(3)
C(5) – C(6)	1.519(3)
C(5) – C(20)	1.536(3)
C(5) – C(8)	1.563(3)
O(6) – C(6)	1.196(2)
C(8) – N(13)	1.459(2)
C(8) – C(9)	1.526(3)
C(9) – C(10)	1.516(3)
C(10) – C(11)	1.507(4)
C(11) – C(12)	1.498(4)
C(12) – N(13)	1.478(3)
N(13) – C(14)	1.407(3)
C(14) – C(19)	1.398(3)
C(14) – C(15)	1.411(3)
C(15) – C(16)	1.372(4)
C(16) – C(17)	1.375(4)
C(18) – C(19)	1.387(3)
C(17) – C(18)	1.374(3)
C(19) – C(20)	1.497(3)

Table 25 Bond Angles (degrees)

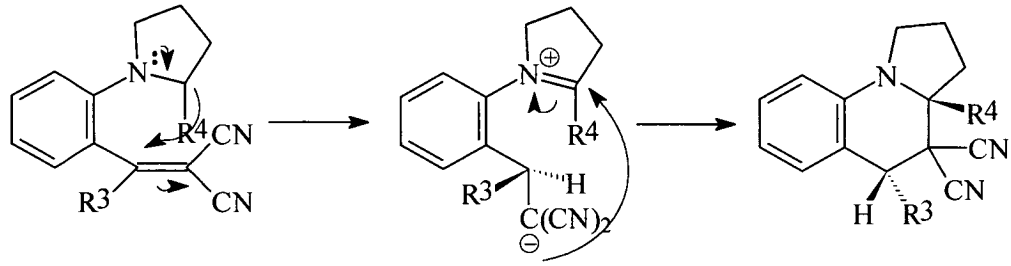
C(6) – O(1) – C(2)	120.55(14)
O(3) – C(2) – O(1)	110.01(14)
O(3) – C(2) – C(22)	109.71(16)
O(1) – C(2) – C(22)	110.92(16)
O(3) – C(2) – C(21)	106.52(17)
O(1) – C(2) – C(21)	106.18(17)
C(22) – C(2) – C(21)	113.34(18)
C(4) – O(3) – C(2)	118.64(15)
O(4) – C(4) – O(3)	118.07(18)
O(4) – C(4) – C(5)	122.45(17)
O(3) – C(4) – C(5)	119.35(16)
C(6) – C(5) – C(4)	114.16(16)
C(6) – C(5) – C(20)	110.12(15)
C(4) – C(5) – C(20)	108.94(15)
C(6) – C(5) – C(8)	110.61(15)
C(4) – C(5) – C(8)	104.71(14)
C(20) –C(5) – C(8)	108.02(15)
O(6) – C(6) – O(1)	118.12(17)
O(6) – C(6) – C(5)	123.86(17)
O(1) – C(6) – C(5)	118.00(16)
N(13) – C(8) – C(9)	110.33(17)
N(13) – C(8) – C(5)	112.69(15)
C(9) – C(8) – C(5)	111.25(16)
C(10) – C(9) – C(8)	110.89(19)
C(11) – C(10) – C(9)	108.8(2)
C(12) – C(11) – C(10)	112.0(2)
N(13) – C(12) – C(11)	113.3(2)
C(14) – N(13) – C(8)	117.47(15)
C(14) – N(13) – C(12)	114.75(17)
C(8) – N(13) – C(12)	110.99(16)
C(19) – C(14) – N(13)	121.54(16)
C(19) – C(14) – C(15)	116.97(19)
N(13) – C(14) – C(15)	121.43(18)
C(16) – C(15) – C(14)	121.0(2)
C(15) – C(16) – C(17)	121.6(2)
C(18) – C(17) – C(16)	118.0(2)
C(17) – C(18) – C(19)	121.9(2)
C(18) – C(19) – C(20)	117.90(18)
C(14) – C(19) – C(20)	121.69(17)
C(19) – C(20) – C(5)	113.81(16)
C(18) – C(19) – C(14)	120.38(18)

The general reaction of the tertiary amino effect to a vinyl moiety is shown in **Scheme 132**, where compound **340** results in compound **341**.



340 **Scheme 132** **341**

Reinhoudt and Verbroom found that the cyclisation to give 6-membered rings occurs when there are two electron-withdrawing groups at the β-position of the vinyl moiety (R^1 and R^2), but when there was one electron-withdrawing group at this position no reaction took place.[110] In most cases these groups were cyano groups. These cyclisation reactions were carried out by heating the appropriate derivative **340** to reflux in either toluene, 1-butanol or mesitylene. The proposed mechanism for this reaction is shown in **Scheme 133.**



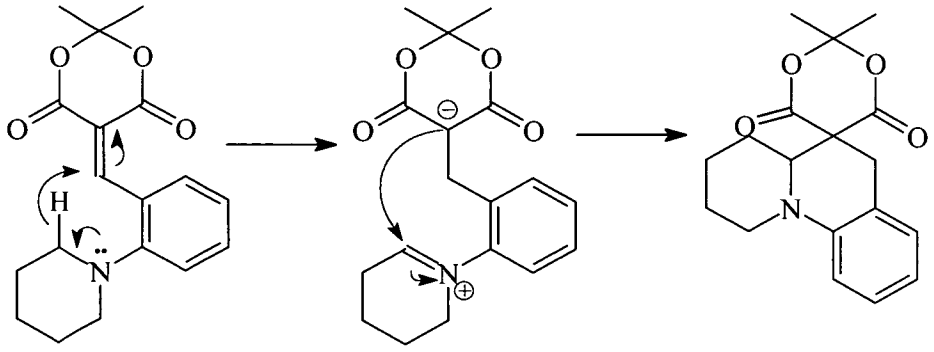
342 **343** **344**

Scheme 133

Compound **342** undergoes an intramolecular hydrogen shift to give intermediate **343**. The second step in the reaction involves the formation of a C-C bond (by the addition of the carbanion to the iminium double bond) which is stereochemically well-defined to yield the product **344**.

However, there are some major differences between the findings of Reinhoudt and Verbroom, and these results. In their work, malononitrile was reacted with the appropriate benzaldehyde which, with a few exceptions, could be isolated and then refluxed for several hours in either toluene, 1-butanol or mesitylene for cyclisation to take place. In contrast to this, when Meldrum's acid was used in place of malononitrile, the milder conditions of either stirring overnight in pyridine, or in

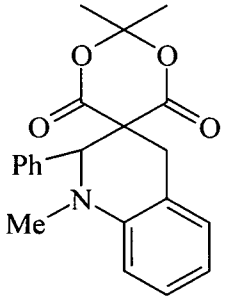
toluene with piperidine and glacial acetic acid, were required for cyclisation to take place, with no isolation of the uncyclised condensation product. The mechanism for the cyclisation of compound **339** is shown in **Scheme 134**.



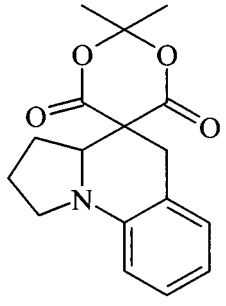
Scheme 134

The milder conditions that are required for this cyclisation can be attributed to the strong electron withdrawing nature of the Meldrum's acid. This must have a stronger effect than the two cyano groups shown in **Scheme 133**.

When compounds **336d** and **336e** were reacted with Meldrum's acid under the second set of condensation conditions (stirring overnight in pyridine), the cyclised compounds **345** and **346** were isolated in 82% and 45% yield respectively. [It should be noted that the first condensation method (stirring overnight in toluene with catalytic amounts of piperidine and acetic acid) was also used for the synthesis of compound **346**, and the yield for this reaction was 40%, suggesting that the second method is preferable for the synthesis of these compounds.]



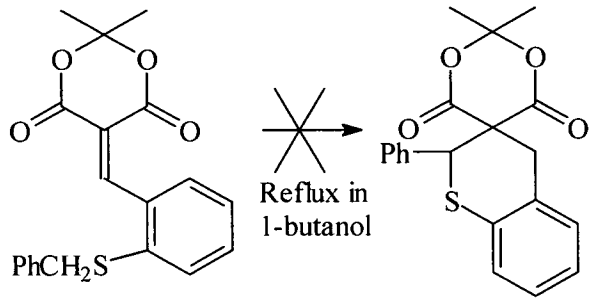
345



346

When 2-(2-methylpiperidin-1-yl)benzaldehyde was reacted with Meldrum's acid under similar conditions, there were no identifiable products by ^{1}H NMR spectroscopy. Again this was attributed to increased steric bulk at the potential reaction centre.

It was attempted to cyclise the analogous sulfur compound **324**, as shown in **Scheme 135**, using the method of Verbroom *et al*, of refluxing in 1-butanol for several hours. However, ^{1}H NMR spectroscopy showed only the presence of uncyclised compound.



324 **347**

Scheme 135

This is further evidence that the sulfur atom does not have enough electron-donating ability and cannot cause the hydride shift needed for compound **324** to cyclise to compound **347**.

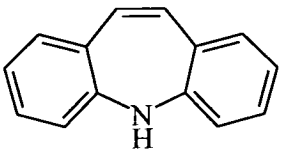
The desired pyrolysis precursors were not obtained in these condensation reactions, but a novel, mild route to functionalised 1,2,3,4-tetrahydroquinolines and 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolines has been discovered. This method could be used for the introduction of a new C-C bond function to a molecule.

C. Pyrolysis of seven-membered heterocycles.

4.1 Preamble.

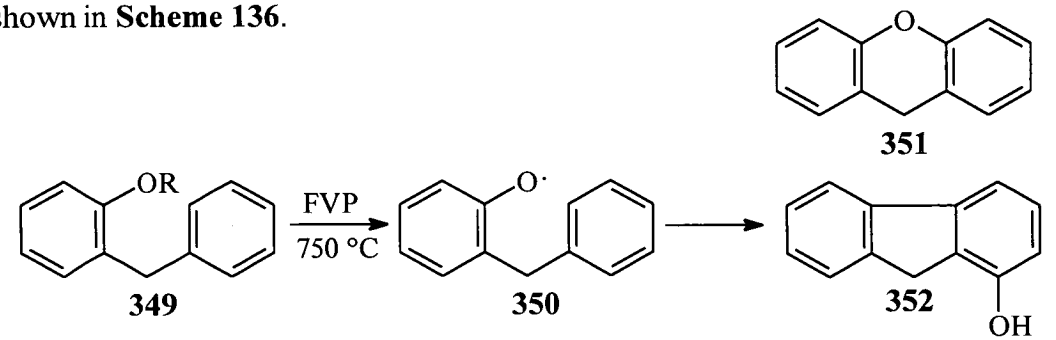
A review of the literature relating to the use of seven-membered heterocycles as precursors in pyrolytic reactions is contained in the introduction. Radical reactions that occur under FVP conditions tend not to have the radical on the heterocyclic nucleus but out on a substituent of the ring system. Radicals on the heterocyclic nucleus such as the *N*-pyrrolyl radical or the *N*-indolyl radical have not been reported in the literature, in reference to gas phase reactions. Therefore it was of interest to see if these could be investigated.

Therefore, 5*H*-dibenzo[*b*,*f*]azepine **348** was chosen as a suitable precursor for investigation in pyrolytic experiments. This compound is the nucleus of a family of compounds which have been widely used in the pharmaceutical industry and its derivatives show antidepressant activity in particular, as well as exhibiting properties of antiallergic, antiepileptic and fungicidal action among others.[111] Azepines tend to be unstable compounds and this is a commercially available one.



348

It was hoped to generate the radical on the nitrogen of the compound **348** by introducing either a benzyl or an allyl group at this position. It has been shown in previous work that both allyl and benzyl groups will cleave under FVP conditions to form radicals.[112] This is shown in **Scheme 136**.



351

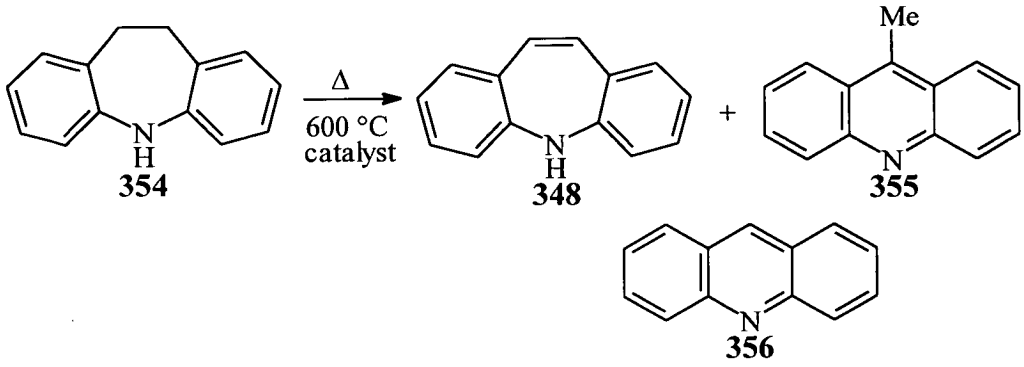
349 **350** **352** **353**

a; R = CH_2Ph
b; R = CH_2CHCH_2

Scheme 136

Compounds **349a** and **349b** produce radical **350** when pyrolysed at 750 °C. This radical then follows several pathways. It cyclises onto the phenyl group to produce **351**, it captures a hydrogen to produce **353** or can rearrange to compound **352**. It should be noted that the benzyl radical formed from the pyrolysis of compound **349a**, will dimerise to give bibenzyl **331** as a side-product. The allyl radical produced in the pyrolysis of compound **349b** results in a gas which is lost in the work-up of the FVP experiment.

It should be noted that the synthesis of compound **348** has been widely investigated in the gas phase and dehydrogenation catalysts have been important mediators in this process.[113, 114] In work by Inoue,[115] the pyrolytic preparation of compound **348** from compound **354** was investigated and is shown in **Scheme 137**.



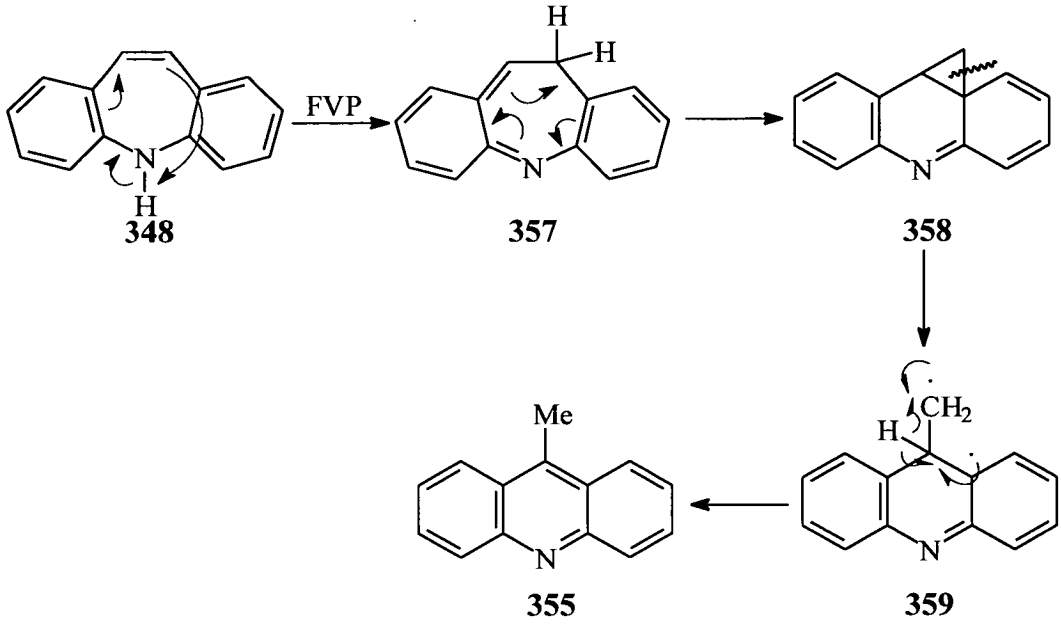
Scheme 137

This reaction was carried out using flow pyrolysis conditions at 600 °C. Cobalt, iron and manganese oxide catalysts were used and gave reasonable conversion to products, with a maximum yield of 41% for 5*H*-dibenzo[*b*,*f*]azepine **348**. 9-Methylacridine **355** and acridine **356** were produced in 5-10% yields as side-products in each case. It is noted that at higher temperatures, the yield of side-products **355** and **356** increases.

Therefore, compound **348** was initially subjected to pyrolysis conditions to investigate the behaviour of the parent system and its alkylated analogues were investigated to see if the nitrogen radical could be generated and if so, whether subsequent ring contraction reactions could occur.

4.2 Pyrolysis of 5*H*-dibenzo[*b,f*]azepine and its *N*-alkylated derivatives.

Compound **348** was subjected to pyrolysis conditions at 950 °C and it underwent a ring contraction reaction to give 9-methylacridine **355** in 60% yield. The proposed mechanism for this reaction is illustrated in **Scheme 138**.

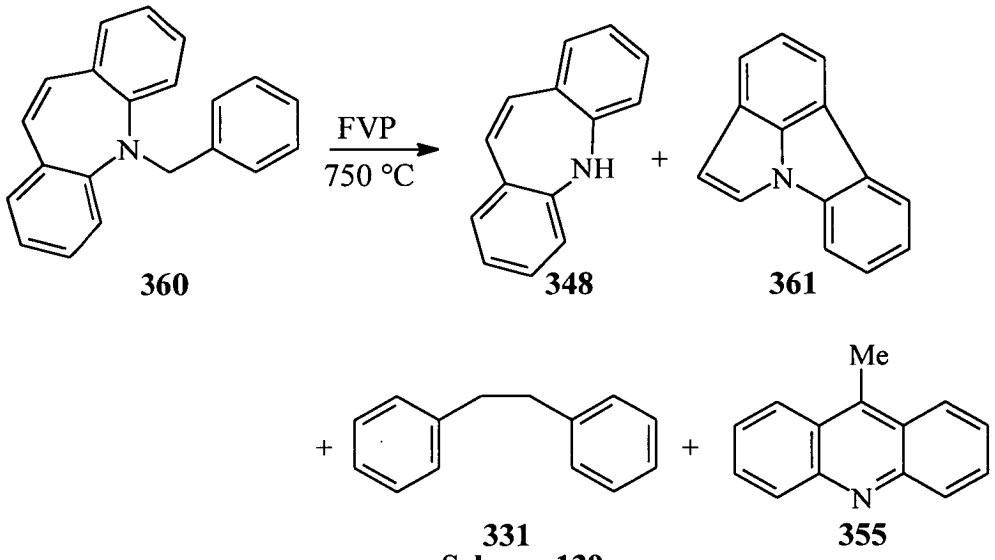


Scheme 138

Initially, there is a 1,5-hydrogen shift from the nitrogen atom to give intermediate **357**. This undergoes an electrocyclisation reaction to form three-membered ring **358**, which will spring open due to ring strain to give intermediate **359** which can rearrange to the stable aromatic acridine **355**. This final step is a [1,2]-hydrogen shift which would be disallowed by the Woodward-Hoffman rules. However, work by Scott and co-workers[116] suggests that these shifts should occur at the higher temperatures used in a flash vacuum pyrolysis experiment. This suggests that the side-products in the synthesis of compound **348** shown in **Scheme 137** are actually pyrolysis products of the 5*H*-dibenzo[*b,f*]azepine **348**. However, the catalyst must be involved in the formation of acridine as there is no straightforward mechanism to rationalise its formation.

In order to synthesise a precursor to the dibenzo[*b,f*]azepin-5-yl radical, 5*H*-dibenzo[*b,f*]azepine was treated with benzyl bromide under the standard conditions of stirring overnight with KOH and DMSO and gave 5-benzyl-5*H*-dibenzo[*b,f*]azepine **360** in 35% yield. This was an extension of the Heaney and Ley[73] method for the alkylation of pyrroles and indoles to the azepine series. When this was subjected to flash

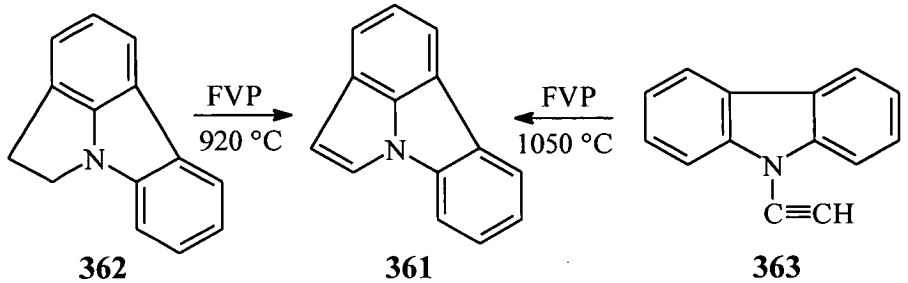
vacuum pyrolysis conditions at 750 °C, there were four products - bibenzyl **331** which would be expected from the dimerisation of the benzyl radical, 5*H*-dibenzo[*b,f*]azepine **349** in 20% yield, which again would be expected from hydrogen abstraction by the nitrogen radical and 9-methylacridine **355** in 2% yield, from the thermal ring contraction of 5*H*-dibenzo[*b,f*]azepine **349** (as previously described). However, the major product was assigned as pyrrolo[3,2,1-*jk*]carbazole **361** (this was produced in a combined yield with bibenzyl of 55%) which is another ring contraction product. A NMR assignment of this compound was carried out and is discussed in **Section 4.3**. The identity of the product was confirmed by comparison with literature spectra.[117] This is shown in **Scheme 139**.



360 **348** **361** **331** **355**

Scheme 139

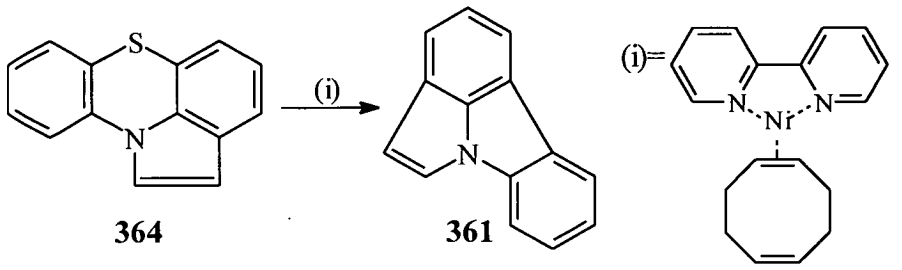
Brown and co-workers[117] have obtained compound **361** using FVP reactions, as shown in **Scheme 140**. Compound **362** can be dehydrogenated to compound **361** in 10% yield, when pyrolysed at 920 °C. 9-Ethynylcarbazole **363** also produces compound **361** under FVP conditions at 1050 °C.



362 **361** **363**

Scheme 140

Hallberg and co-workers[118] have also made this compound *via* a solution phase method. This is shown in **Scheme 141**. Compound **364** undergoes a desulfurisation reaction using a nickel(0) complex, to give compound **361** in 72% yield.

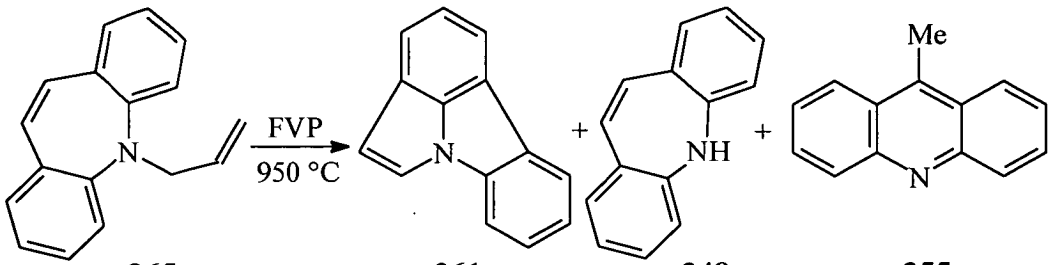


364 **361**

Scheme 141

However, both these methods produce only milligram quantities of compound **361**. The pyrolysis method shown in **Scheme 139** is the first method where larger quantities of compound **361** can be synthesised easily.

In the pyrolysis reaction of compound **360**, shown in **Scheme 139**, bibenzyl **331** and pyrrolo[3,2,1-*jk*]carbazole **361**, proved to be inseparable by chromatography. This purification problem was alleviated by using the allyl group as the radical generator, as outlined in **Scheme 142**.

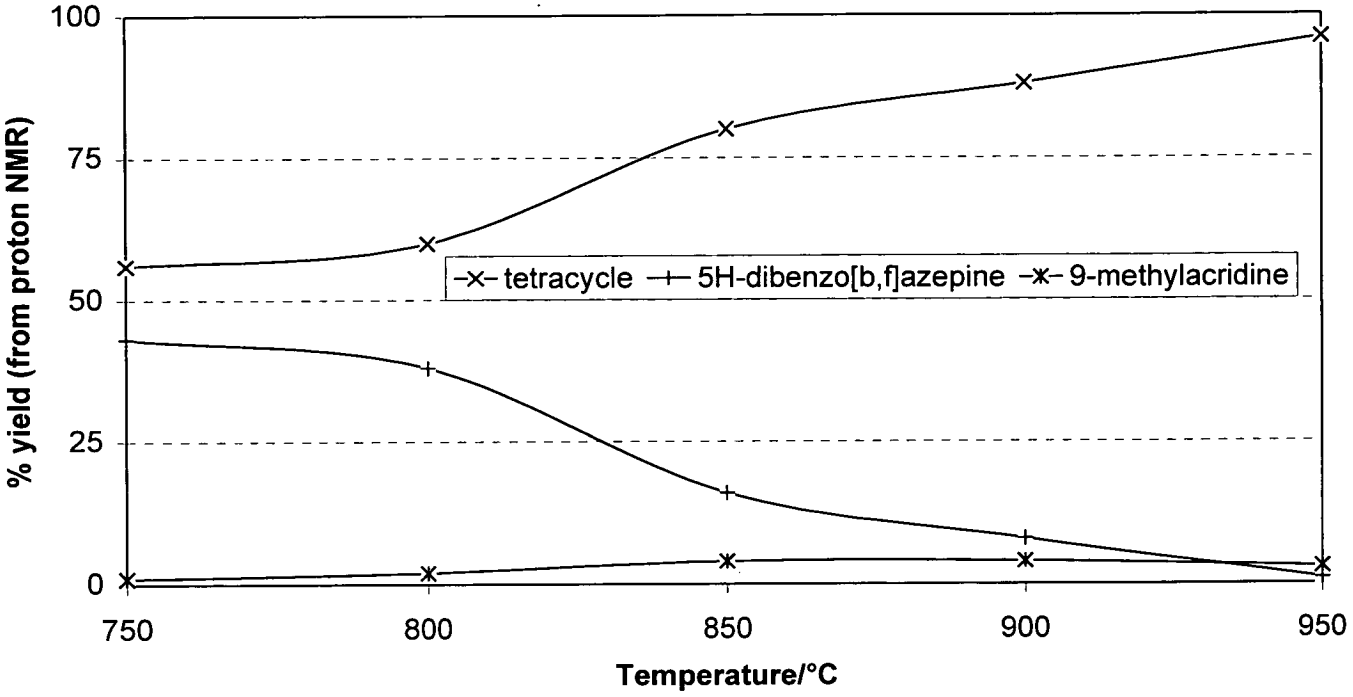


365 **361** **348** **355**

Scheme 142

The 5-allyl-5*H*-dibenzo[*b*,*f*]azepine **365** was synthesised by the same method as the benzylated derivative **360**, and was obtained in 46% yield. This compound was pyrolysed over a range of temperatures from 750 - 950 °C, to find the optimum pyrolysis temperature for compound **361** formation. The temperature of the pyrolysis proved to have a dramatic effect on the amount of compound **361** produced, as shown in **Graph 2**. At higher temperatures, there was more compound **361** formed, and accordingly less 5*H*-dibenzo[*b*,*f*]azepine **349** and 9-methylacridine **350**. The optimum temperature for formation of compound **361** is 950 °C, with a preparative yield of 63% after chromatography on a 1.1 g scale.

Graph 2- Temperature Dependence of Tetracycle Formation.



The plots for 5*H*-dibenzo[*b,f*]azepine and 9-methylacridine cross at 930 – 940 °C and this suggests that the 5*H*-dibenzo[*b,f*]azepine is being forced to ring contract at these temperatures as previously observed.

4.3 NMR assignment of pyrrolo[3,2,1-*jk*]carbazole.

Compound **361** was subjected to NMR experiments, and the ^{1}H and ^{13}C were fully assigned *via* a proton-carbon correlation. Compound **361** and its numbering system are shown in **Figure 29**. This confirmed the partial assignment by Klingstedt and co-workers.[118]

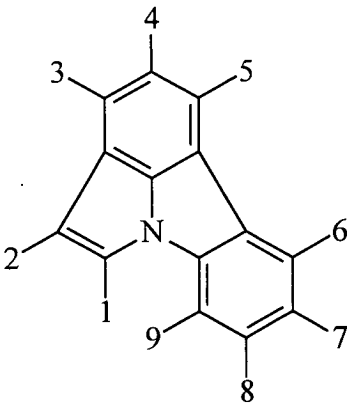


Figure 29

The ^{1}H NMR spectrum is shown in **Figure 30** and was fully assigned.

The triplet at 7.57 ppm, which shows only *ortho* couplings was assigned unambiguously as the 4-proton. The 4-proton can only couple to the 3-and 5-protons which are adjacent to it, which would explain the aforementioned coupling pattern. Therefore, the doublets at 7.95 ppm and 7.85 ppm, which show only *ortho* couplings and have the same coupling constants as displayed in the 4-proton signal, must be due to the protons in the 3- and 5-positions, but which signal was due to which proton could not be assigned from this spectrum alone. The doublets at 6.91 ppm and 7.77 ppm, with a small coupling constant of 3.1 Hz, were assigned as due to the 1- and 2-protons. These two protons can only couple to each other, which explains their multiplicity. In *N*-phenylindole, the coupling constant for the 2- and 3-protons is 4.7 Hz.[119] Again, which signal corresponds to which proton could not be assigned from this spectrum alone. The doublets of doublets of doublets at 8.12 ppm and 7.71 ppm were assigned as the 6- and 9-protons, these being the only protons that will display such a coupling pattern from *ortho*, *meta* and *para* couplings. The triplets of doublets at 7.37 ppm and 7.52 ppm therefore had to be due to the protons in the 7- and 8-positions.

A NOESY experiment showed a correlation between the protons at 6.9 ppm and 7.85 ppm, which suggested that these protons were in close proximity to each other.

Using the information explained above, this suggested that these signals were due to the 2 and 3 protons respectively. There was also a correlation between the protons at 7.95 ppm and 8.12 ppm, which suggested that these were due to protons 5 and 6 respectively. The protons in the 7- and 8- positions could be assigned from their coupling constants. The chemical shift, coupling constant and assignment of each signal is shown in **Table 26.**

δ_H/ppm	Coupling constants/Hz	Assignment	Coupling pattern
8.12	J 7.9, ^4J 1.2, ^5J 0.7	H6	ddd
7.95	^3J 7.4	H5	d
7.85	^3J 7.4	H3	d
7.77	^3J 3.1	H1	d
7.71	^3J 7.9, ^4J 1.0, ^5J 0.7	H9	ddd
7.57	^3J 7.4	H4	t
7.52	^3J 7.9, ^4J 1.2	H8	td
7.37	^3J 7.9, ^4J 1.0	H7	td
6.91	^3J 3.1	H2	d

Table 26:- Proton NMR data for compound **361**.

The proton-carbon correlation spectrum is shown in **Figure 31**. The CH carbon signals could be assigned unambiguously from this, and are shown in **Table 27**.

δc/ppm	Assignment
127.01	C8
123.91	C4
123.62	C6
122.93	C1
122.63	C7
121.54	C3
117.84	C5
111.91	C9
109.86	C2

Table 27:- Carbon NMR data for compound **361**.

An X-ray crystal structure of **361** confirmed the proposed connectivity and is shown in **Figure 32**. However, despite many attempts, crystals of sufficient quality for bond length and angle data could not be obtained.

^{1}H NMR spectrum for compound **361**.

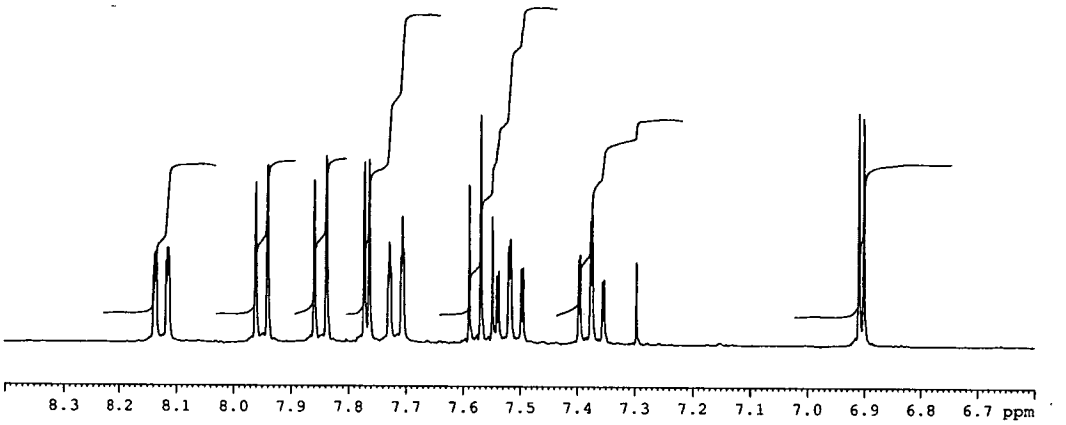


Figure 30

Proton-carbon correlation spectrum for compound **361**.

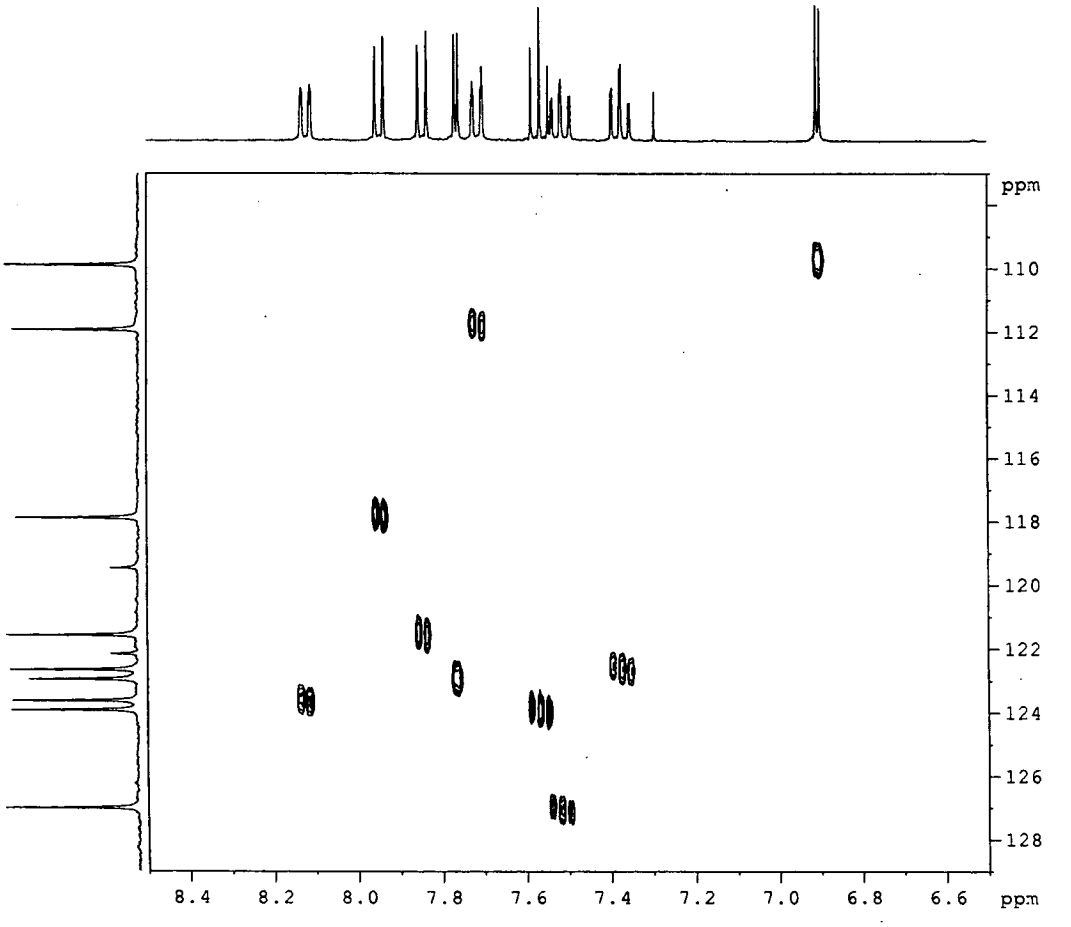


Figure 31

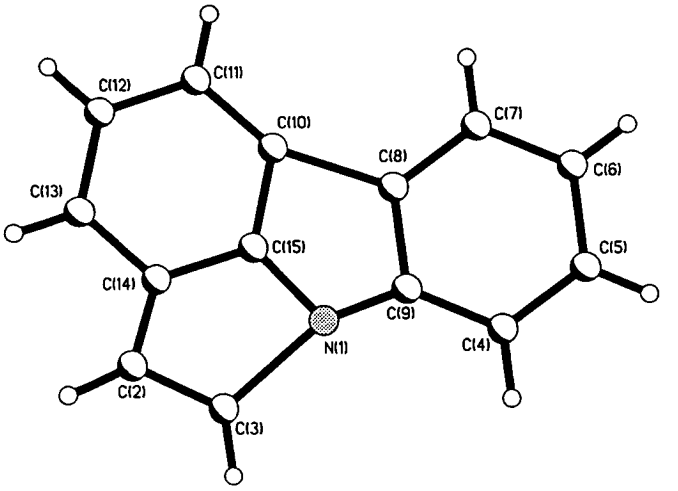
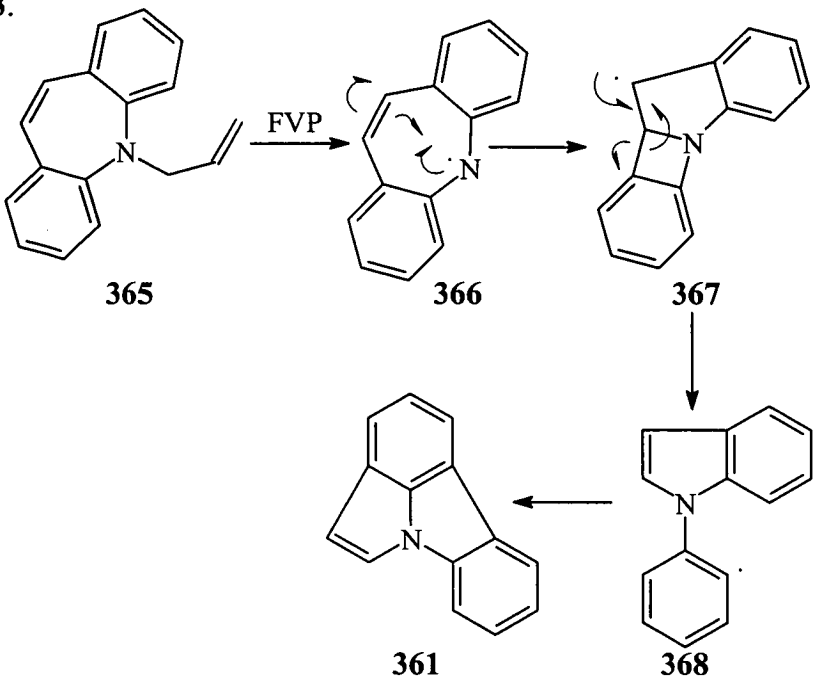


Figure 32

The proposed mechanism for the formation of this tetracycle **361** is illustrated in **Scheme 143**.



365 **366** **367** **361** **368**

Scheme 143

Flash vacuum pyrolysis of compound **365** causes the loss of the allyl radical to give nitrogen radical **366**. This radical attacks the double bond of the seven-membered ring to form a strained four-membered ring **367**. This may be an intermediate or a transition state. This will spring open to form phenyl radical **368** which cyclises with the loss of a hydrogen atom to give compound **361**. Phenyl radical **368** seems to be a key intermediate in the formation of **361**, and this is discussed further in **Sections D** and **E**.

The pyrolytic synthesis of compound **361**, shown in **Scheme 139**, allowed larger quantities to be made for the first time and therefore some of its chemical properties were investigated for the first time.

4.4 Chemical Properties of Pyrrolo[3,2,1-*jk*]carbazole.

Compound **361** is an interesting compound as it can be viewed as a carbazole or as an indole, as shown in **Figure 33**.

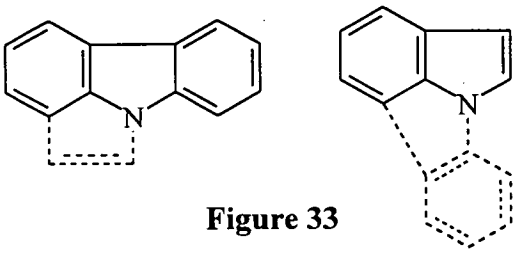


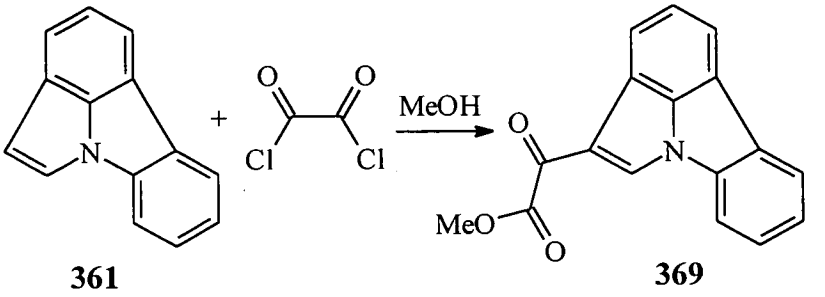
Figure 33

Compound **361** could potentially act as either an indole or as a carbazole in its chemical reactions. To investigate this, compound **361** was reacted with a series of electrophiles (which are known to react with indoles).[120]

In all cases a low yield was obtained with no recovered compound **361** which suggests that compound **361** is extremely reactive and decomposes under the reaction conditions.

4.4.1 With oxalyl chloride

Compound **361** was treated with oxalyl chloride and then methanol. This resulted in compound **369** in 48% yield.



361 **369**

Scheme 144

The proton spectrum for compound **369** is shown in **Figure 34**. This suggested that substitution had taken place in the 2-position. The proton spectrum of compound **361** has a doublet below 7.0 ppm, which has been assigned as the 2-position in the spectrum and this is absent in the spectrum of compound **369**. This observation was confirmed by a NOESY NMR experiment, the spectrum of which is shown in **Figure 35.** If the tetracycle was 1-substituted, a correlation of proton 2 to proton 3 would be expected.

^{1}H NMR spectrum for compound **369**.

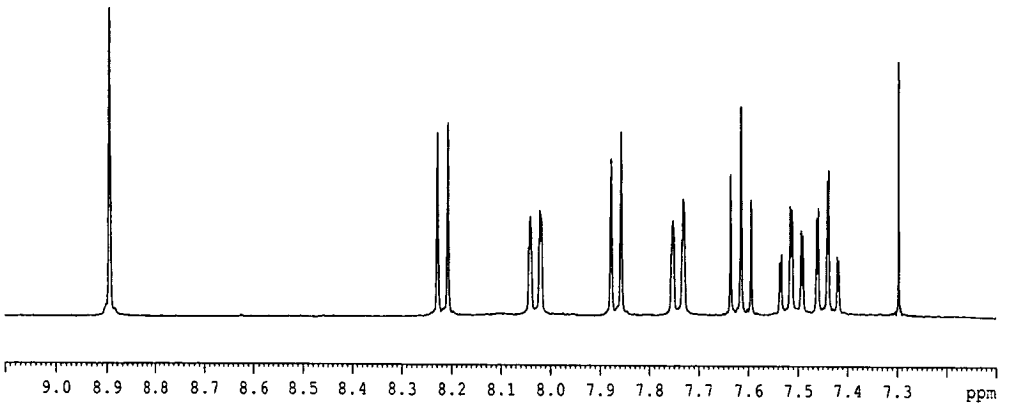


Figure 34

NOESY plot for compound **369**.

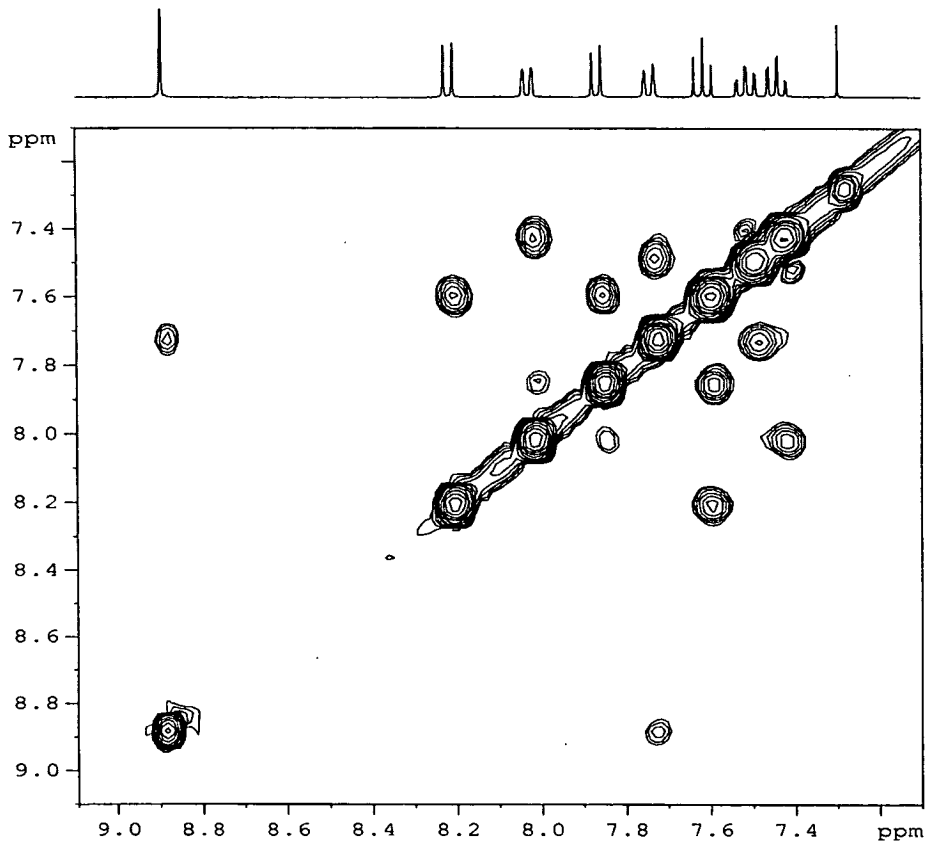
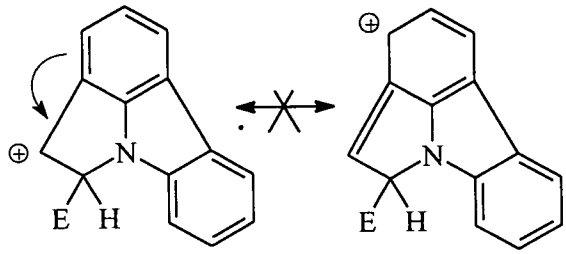


Figure 35

For 2-substitution, a correlation of proton 1 to proton 9 would be expected. The singlet at ~8.9 ppm must be due to the uncoupled 1- or 2-proton. It shows one correlation corresponding to the triplet of doublets at ~7.7 ppm, which has been unambiguously assigned as proton 9. This confirms that 2-substitution occurs. This can be assigned in two ways; firstly, the multiplicity of this signal suggests that it corresponds to proton 9, which is a doublet of doublet of doublets. This corresponds to a proton with *ortho*, *meta* and *para* couplings. Proton 3 is a doublet with an *ortho* coupling from proton 4 and occurs at ~7.8 ppm. Secondly, proton 9 occurs at 7.71 ppm in compound **361**, which is a similar chemical shift to this signal.

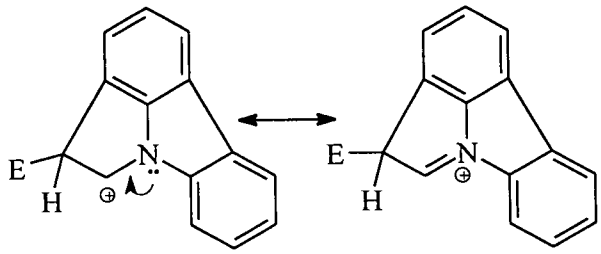
Substitution at the 1-proton and at the 2-proton sites of compound **361** are shown in **Schemes 145** and **146**, respectively.



Scheme 145

If substitution occurred at the 1-position, as shown in **Scheme 145**, then resonance stabilisation of the cation intermediate would require the aromaticity of the benzene ring to be broken which would be unfavourable.

However, if substitution took place at the 2-position, as shown in **Scheme 146**, resonance stabilisation of the cation intermediate does not require the aromaticity of the benzene ring to be broken and is more favourable. This could account for the substitution pattern of this compound.

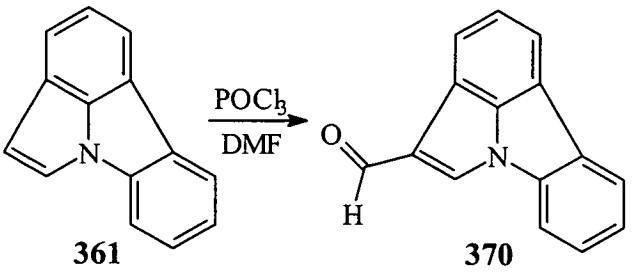


Scheme 146

This explanation is identical to the rationalisation of indole substitution patterns suggesting that compound **361** acts as an indole in its reaction with oxalyl choride.

4.4.2 Vilsmeier Reaction.

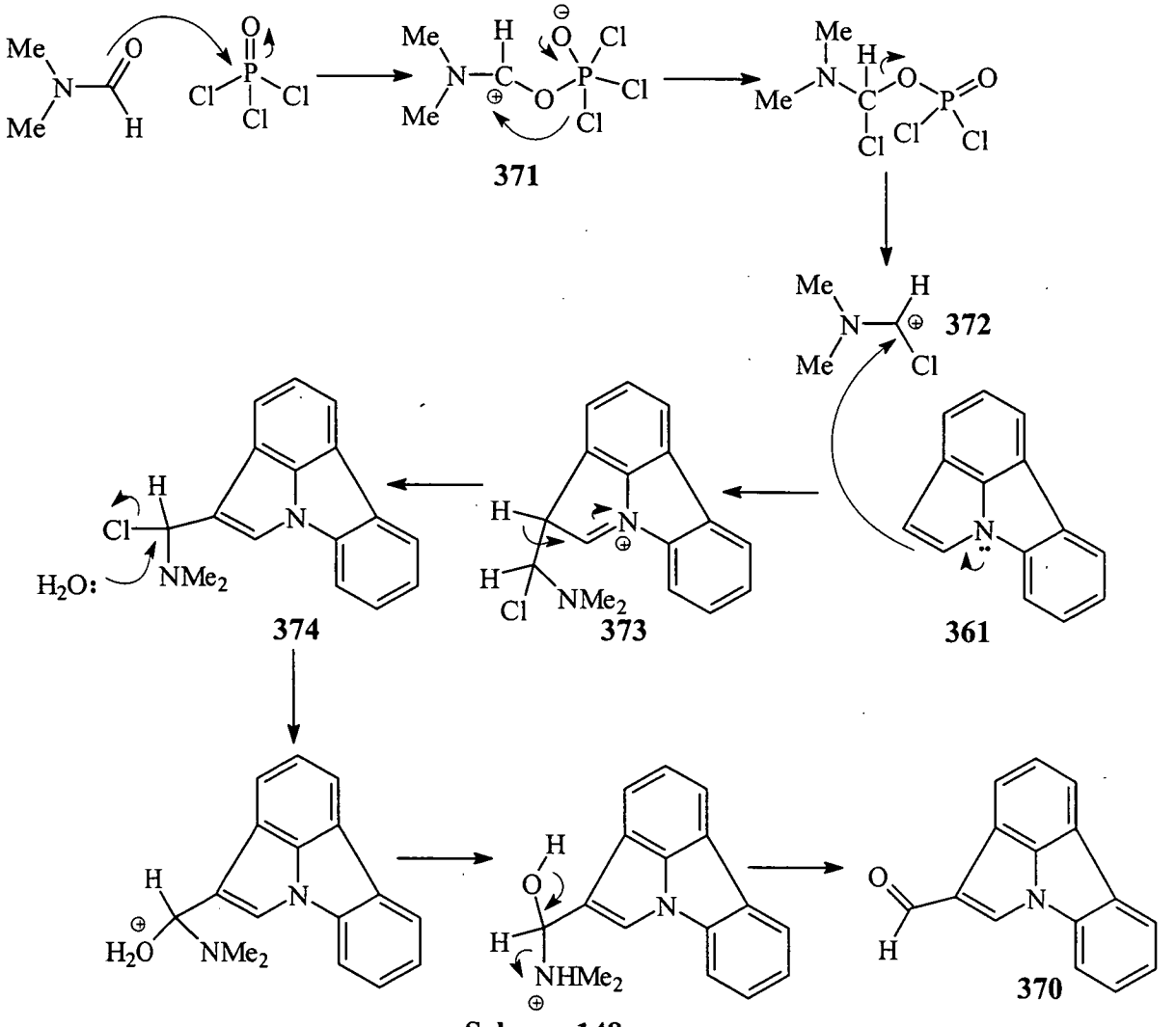
Pyrrolo[3,2,1-*jk*]carbazole **361** was treated with $POCl_3$ in DMF and resulted in compound **370** in 15% yield, as shown in **Scheme 147**. The substitution also occurred in the 2-position and can be rationalised as above. This confirms that compound **361** acts as an indole in its reactions.



361 **370**

Scheme 147

The proposed mechanism for this reaction is shown in **Scheme 148**.

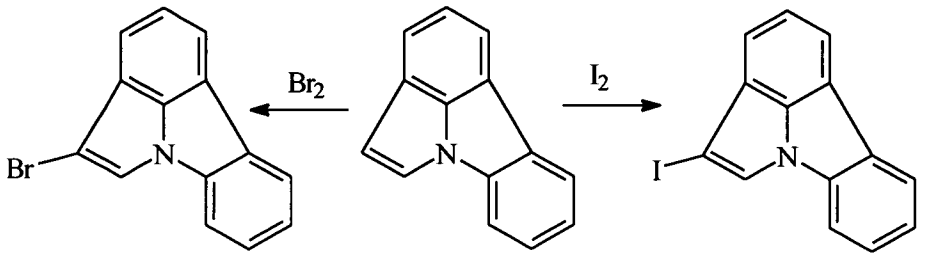


Scheme 148

DMF and phosphorus oxychloride react to form the complex **371**. This can rearrange to give the cation **372** which then reacts with compound **361** to form intermediate **373**. Intermediate **373** will rearrange to the more stable **374** and hydrolysis of this complex forms **370**.

4.4.3 Halogenation Reactions.

Halogenation reactions of compound **361** were carried out using a literature procedure[121] for the halogenation of indole and compounds **375** and **376** were isolated in 21% and 34% yield respectively, as shown in **Scheme 149**.



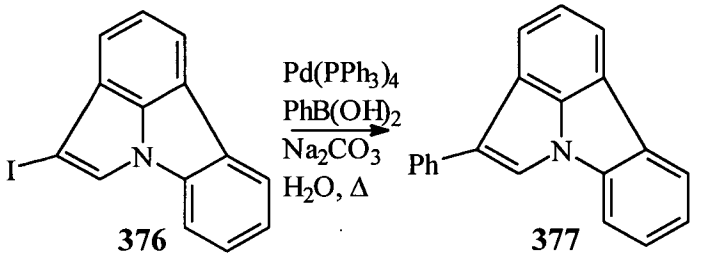
375 **361** **376**

Scheme 149

It should be noted that compounds **375** and **376** are susceptible to decomposition when left at room temperature overnight. However, these decomposition pathways were not investigated.

4.4.4 Suzuki Reaction of Compound 376.

Compound **376** was further reacted in a Suzuki coupling reaction with phenyl boronic acid and resulted in compound **377** in 22% yield. The general reaction is shown in **Scheme 150**.



376 **377**

Scheme 150

The successful nature of this Suzuki reaction suggests that compound **376** can be further reacted although in low yield.

4.4.5 Attempted Reaction with Other Electrophiles.

1. 2,2-Dimethyl-5-methoxymethylene-1,3-dioxane-4,6-dione (MMMA).

MMMA is a mild C-electrophile which has been previously used in the investigation of heterocycles with electrophiles.[20] Under standard conditions, in an acetonitrile solution, there was no evidence that the tetracycle **361** underwent any reaction with MMMA, even after several hours at elevated temperatures.

2. TFA.

TFA has been used in the protonation of heterocycles. However, when compound **361** was placed in TFA, there was immediate decomposition of compound **361** which could not be overcome.

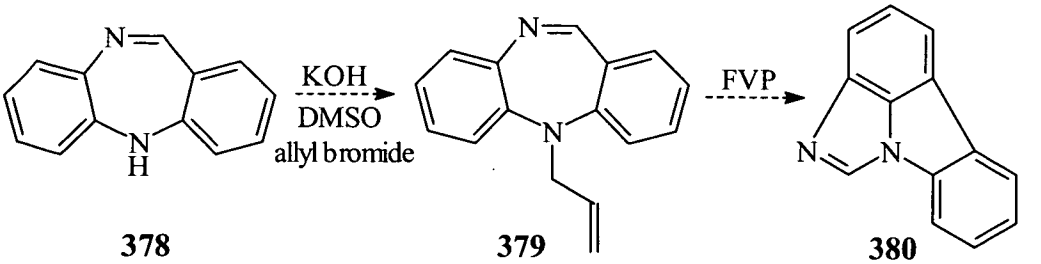
4.4.6 Electrochemistry.

Substituted indoles have been investigated as fluorescent polymer films.[122] When electrochemically oxidised, they form a cyclic asymmetric trimer which is deposited on the electrode surface, forming a conducting film. The trimer molecule is highly fluorescent and therefore has potential uses, as optical sensors and for the direct oxidation and reduction of biomolecules.[123, 124] Redox properties of these trimers can be tuned, and therefore it was of interest to extend this to the study of indole-like systems.

In collaboration with Dr A.R. Mount and Miss M. Chapman, compound **361** was electro-oxidised at a platinum electrode and a film was formed. This film appeared to be less conducting than an indole trimer film, but was redox active and highly fluorescent. At this stage, the material formed on electro-oxidation has not been characterised, but is being investigated.

4.5 Attempted Synthesis of 5*H*-dibenzo[*b*,*f*]diazepine.

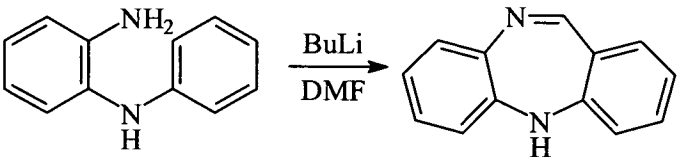
Compound **348** undergoes a pyrolytic ring contraction reaction to give compound **361**, and it was hoped to extend this work to analogues of compound **348**. It was anticipated that compound **379** would pyrolyse to give compound **380**, as shown in **Scheme 151**. Compound **379** could be obtained by the allylation of compound **378**.



378 **379** **380**

Scheme 151

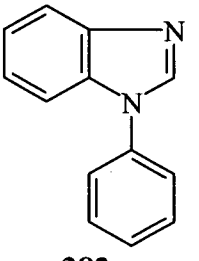
The literature synthesis of compound **378** is shown in **Scheme 152**.[125]



381 **378**

Scheme 152

The authors report that compound **381** was treated with butyllithium and DMF, and after work-up resulted in compound **378**. However, when this was repeated, the obtained product gave an identical proton spectrum and a melting point similar to those reported for compound **378**, although the ^{13}C NMR spectrum did not correspond to this product. The product from this reaction was initially identified as *N*-phenylbenzimidazole due to the presence of a phenyl group on the carbon NMR spectrum. This was confirmed by comparison with literature spectra.[81] This was formed by *N*-formylation, instead of *C*-formylation, followed by attack at the carbonyl group to generate the benzimidazole nucleus.



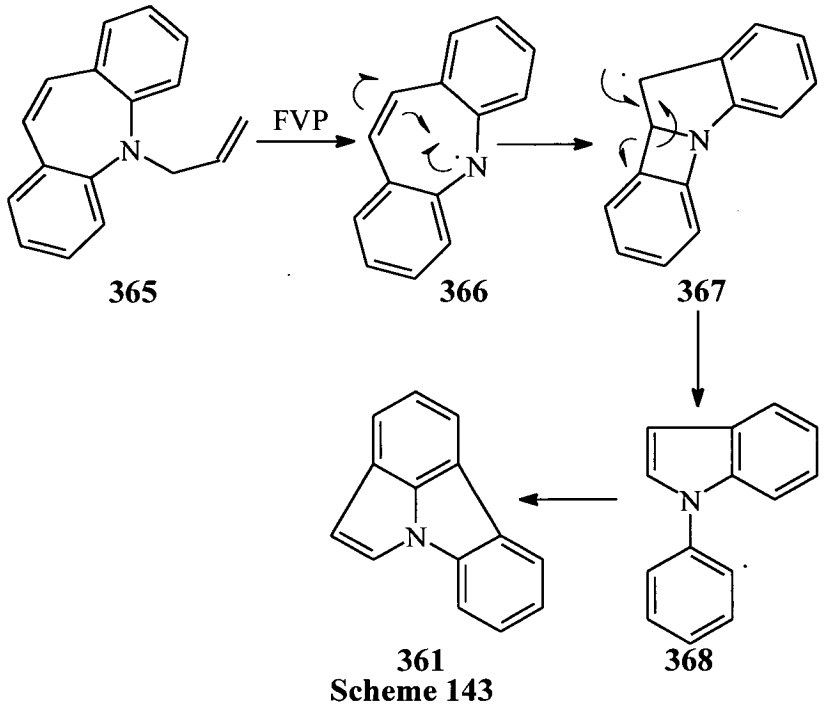
382

Other syntheses to analogues of compound **348** proved to be multistep processes. Therefore an alternative strategy to the synthesis of compounds, such as **361**, was taken and is discussed in **Sections D** and **E**.

D. The Use of the Allyl Ester as an Aryl Radical Generator.

5.1 Preamble.

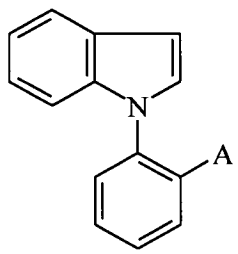
The pyrolytic formation of compound **361** from compound **365**, as shown in **Scheme 143**, was discussed in **Section C**.



Scheme 143

The phenyl radical **368** seems to be a key intermediate in this mechanism. If an alternative method of generating this radical was used, and compound **361** was formed, this would support the proposed mechanism shown in **Scheme 143**. This could also provide a more general route to compounds such as **361**, given that analogues of compound **365** are difficult to synthesise. (see **Section C4.5.**)

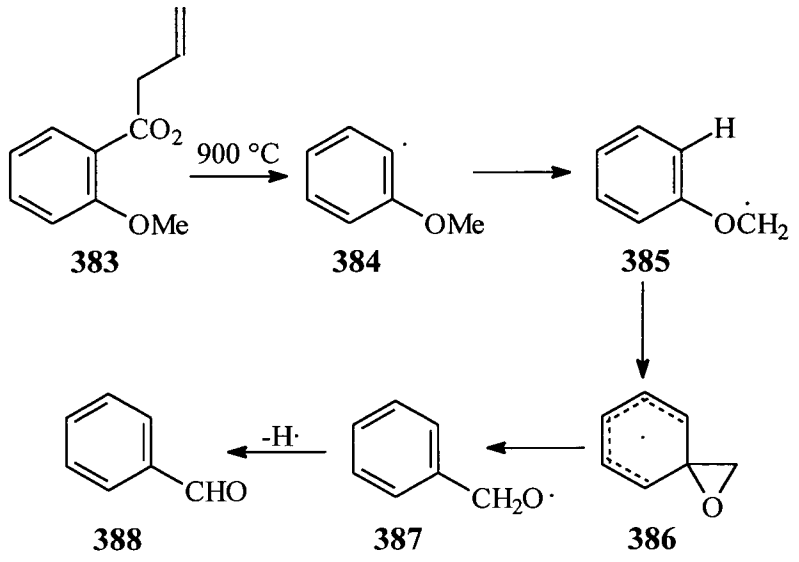
Therefore, a functional group which would result in a phenyl radical when subjected to FVP conditions was needed in the *ortho* position, as shown in **Figure 36**.



A= aryl radical generator.

Figure 36

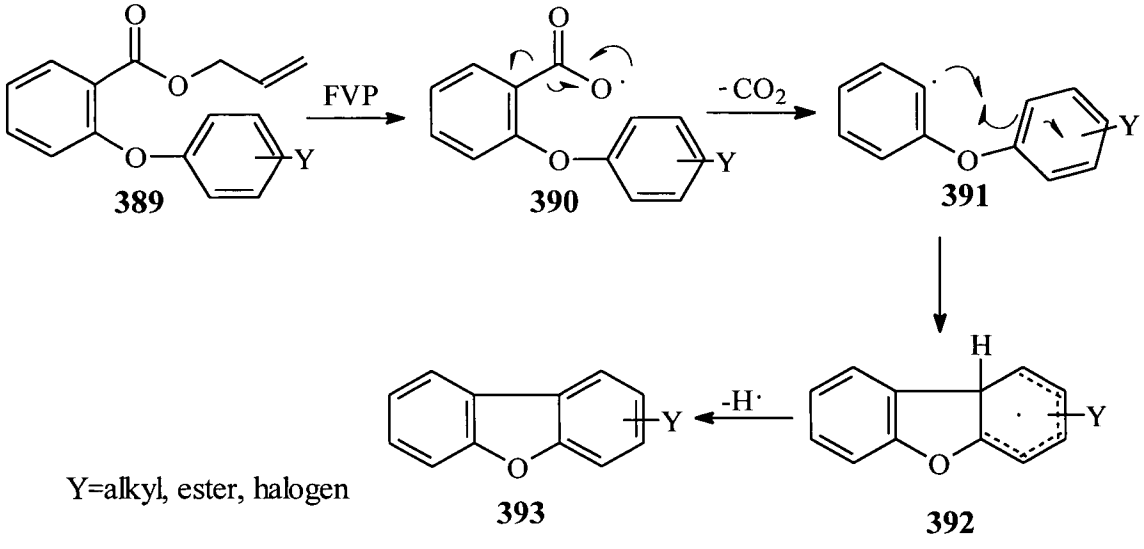
Work by De Mayo[89] has shown that the allyl ester **383** results in the phenyl radical **384**, when pyrolysed at 900 °C, as shown in **Scheme 153**. In this particular example, radical **384** can abstract a hydrogen atom from the methoxy group to give radical **385**. This forms the three-membered ring **386** and breaks in the opposite sense to give intermediate **387**. Loss of a hydrogen atom results in benzaldehyde **388**.



383 **384** **385** **388** **387** **386**

Scheme 153

This work was extended by McNab and co-workers[126] who have shown that the pyrolysis of compound **389** results in compound **393** *via* phenyl radical **391**, as shown in **Scheme 154**.



389 **390** **391** **392** **393**

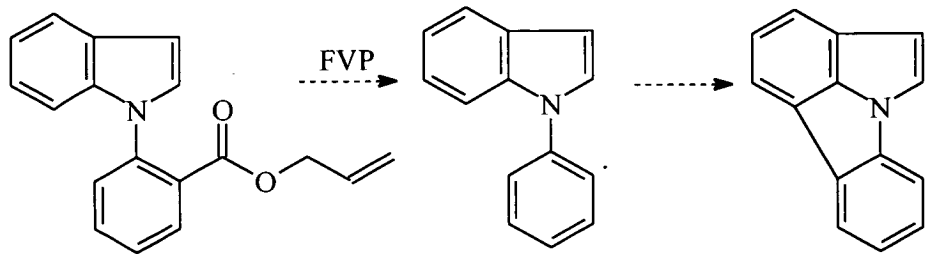
Y=alkyl, ester, halogen

Scheme 154

Compound **389** initially loses the allyl radical to form radical **390**, which subsequently loses carbon dioxide. This results in phenyl radical **391** which cyclises to give radical **392**. Loss of a hydrogen atom forms **393**.

5.2 Synthesis and Pyrolysis of Allyl 2-Indol-1-ylbenzoate.

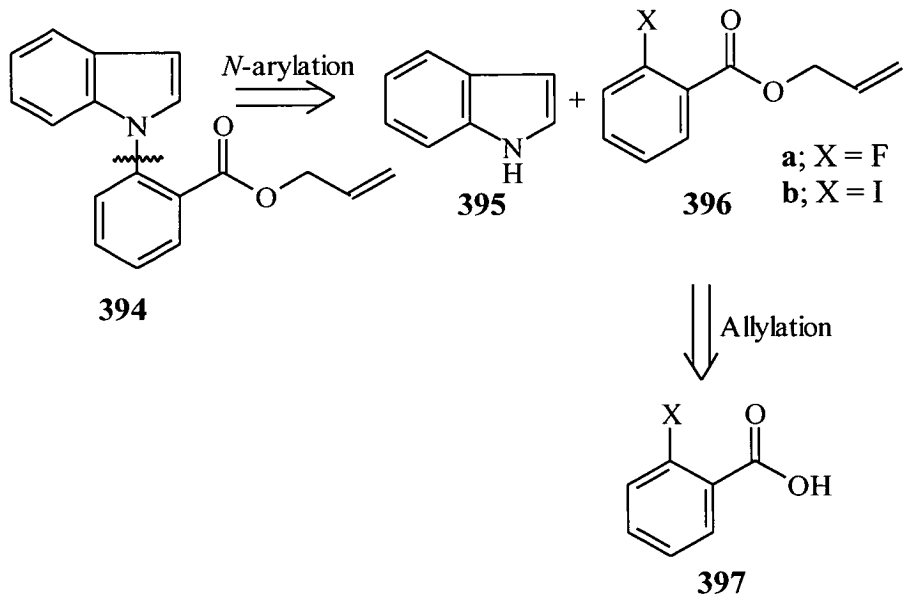
Compound **394** became a target compound, as it would be expected to give the phenyl radical **368** when pyrolysed. This would result in compound **361**, if radical **368** was an intermediate in the mechanism as proposed in **Scheme 143**.



394 **368** **361**

Scheme 155

It was anticipated that compound **394** could be synthesised from indole **395**, and the appropriate allyl ester **396a** or **396b** in an *N*-arylation reaction, as shown in **Scheme 156**.

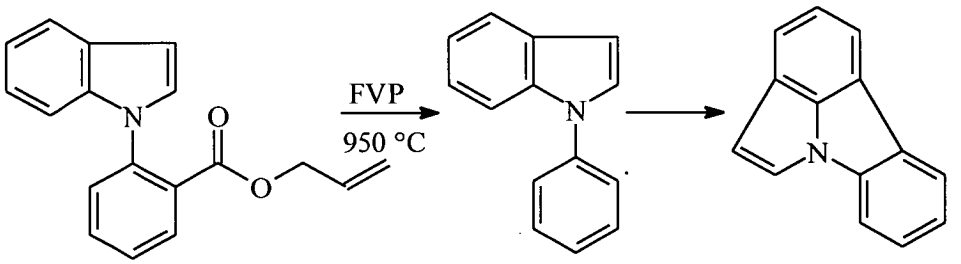


394 **395** **396** **397**

Scheme 156

Several different methods are described in the literature for this type of *N*-arylation reaction, including Ullmann condensations,[127] palladium and copper catalysed reactions[128] (using indole **395** and esters **396a** and **396b** as substrates).

These methods were all investigated, and in each case the desired product was not produced, with recovery of only unreacted starting materials. This may be attributed to the poor nucleophilic character of indole. It was hoped that using the *o*-halobenzoic acid **397** in place of the corresponding allyl ester **396**, would alleviate any steric factors that were preventing the *N*-arylation reaction from taking place. A literature route[127] to this aromatic acid, which involved heating the two substrates in pyridine with K_2CO_3 was carried out, but all attempts to isolate the acid were unsuccessful owing to its solubility and partition properties. (It should be noted that attempts to repeat several syntheses from this paper were unsuccessful). The problem of isolating the acid was overcome by a modification of this method. This was done by the *in situ* allylation of the acid, and compound **394** was obtained in 47% yield. Ester **394** was subjected to FVP conditions at 950 °C and produced compound **361** in 42% yield, as shown in **Scheme 157**.

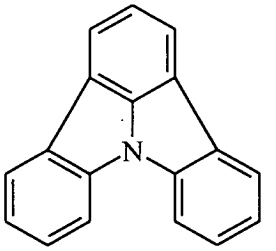


394 **368** **361**

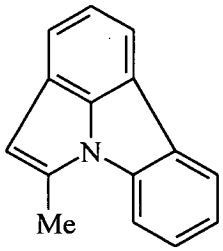
Scheme 157

This result is consistent with phenyl radical **368** being a key intermediate in the pyrolysis reaction of 5-allyldibenzo[*b,f*]azepine **365**, as shown in **Scheme 143**.

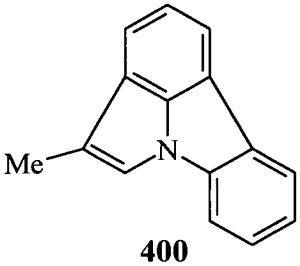
As this pyrolysis was successful, it was anticipated that this route could be made more general and other targets were identified. The simplest way of extending this synthesis, was to replace the indole system with other heterocyclic systems such as carbazole, 2-methylindole, 3-methylindole and benzimidazole. The corresponding pyrolysis products **398**, **399**, **400** and **380** could potentially be made by this route.



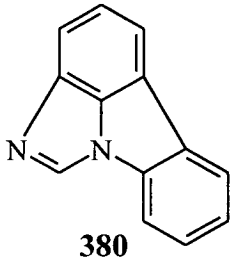
398



399



400



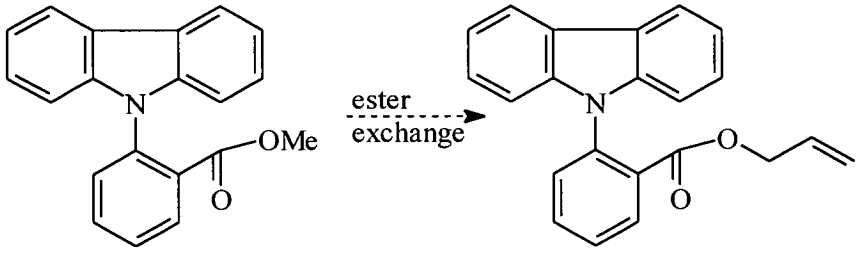
380

5.3 Synthesis of Allyl Ester Precursors.

The *N*-arylation method described above for indole was carried out using carbazole, 2-methylindole and 3-methylindole in place of the indole, and in every case the unreacted starting material was recovered with no desired product. The unsuccessful nature of these reactions was attributed to the increased steric bulk around the *N*-arylation site. Therefore, an alternative strategy was sought for the synthesis of these allyl esters.

5.3.1 Carbazole Analogue.

The methyl ester **401** is a literature[129] compound, and in principle could be subjected to an ester exchange reaction to give the appropriate allyl ester **402**, as shown in **Scheme 158**.

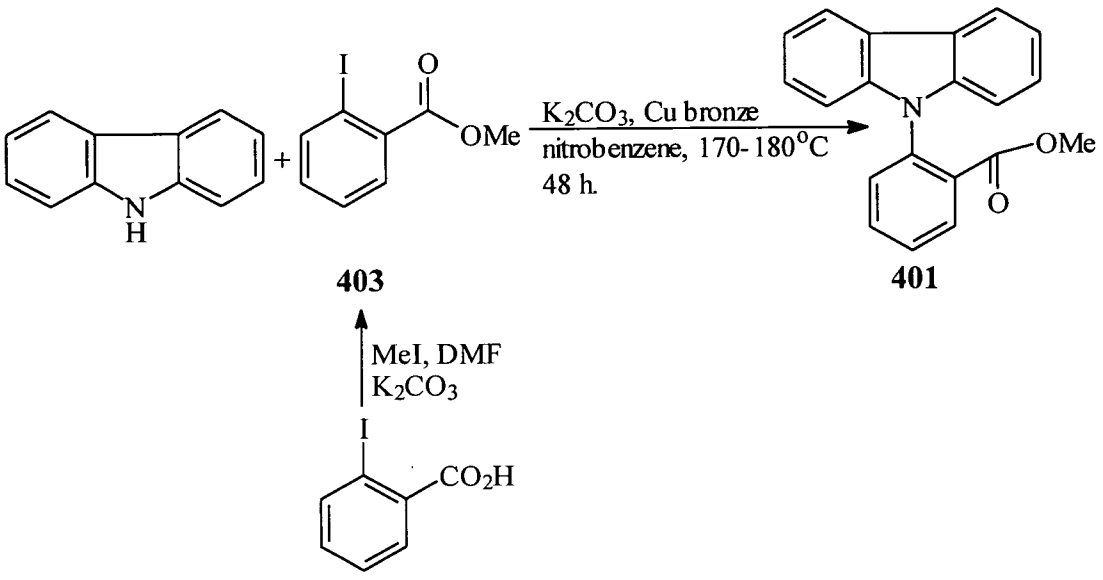


401 **402**

Scheme 158

The methyl ester **401** was synthesised in 46% yield. This was done by heating carbazole with the methyl ester **403** in nitrobenzene with copper bronze and potassium carbonate at 170 °C for 48 h. The methyl ester **403** was itself synthesised

in 84% yield by reacting *o*-iodobenzoic acid with iodomethane, using the standard DMF/K_2CO_3 alkylation conditions. This is shown in **Scheme 159**.



Scheme 159

The success of this reaction suggested, that for this *N*-arylation reaction to take place, forcing conditions were required. It should be noted, that attempts to use the corresponding allyl ester in place of the methyl ester **403** using these reaction conditions, failed to give the desired product. The allyl ester was not recovered from the reaction mixture suggesting that it decomposes under the harsh reaction conditions.

The structure of compound **401** was confirmed by X-ray crystallography and is shown in **Figures 37** and **38** with the corresponding data in **Tables 28** and **29**. The structure of compound **401** proved to be unusual, in that there were eight independent structures of compound **401** in each unit cell. [For the purposes of this discussion, only one configuration is discussed.] This structure is discussed in **Section 5.4**.

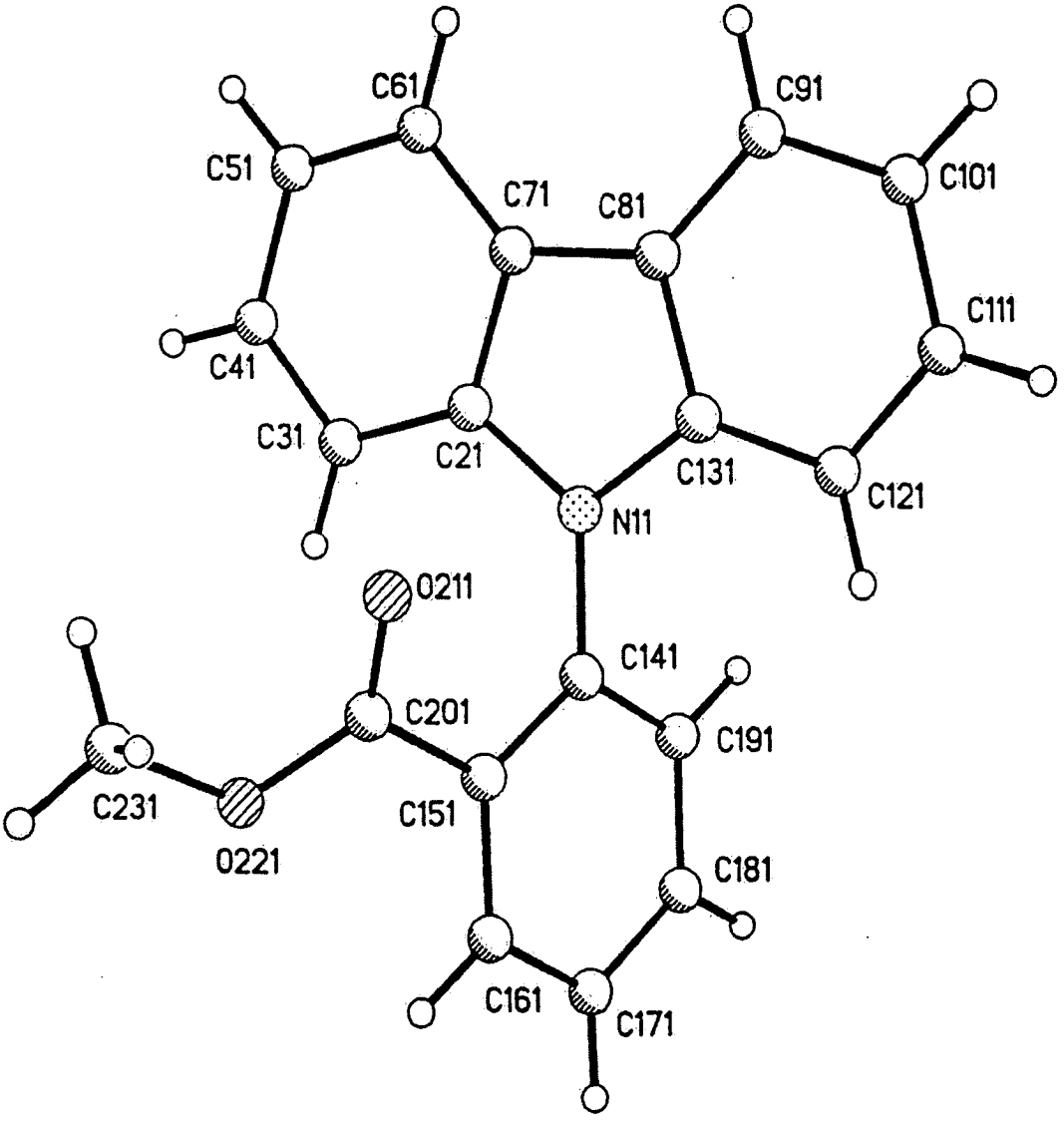

C61
C91
C51
C101
C71
C81
C111
C41
C31
C21
C131
C121
N11
O211
C141
C201
C191
C231
C151
O221
C181
C161
C171

Figure 37

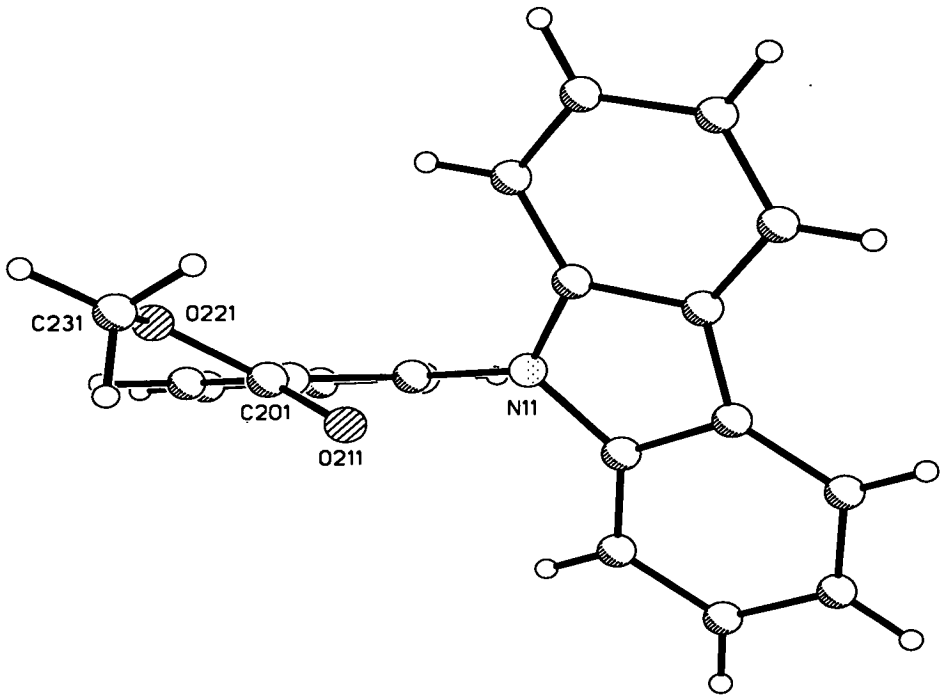


Figure 38

Table 28 Bond Lengths (Å)

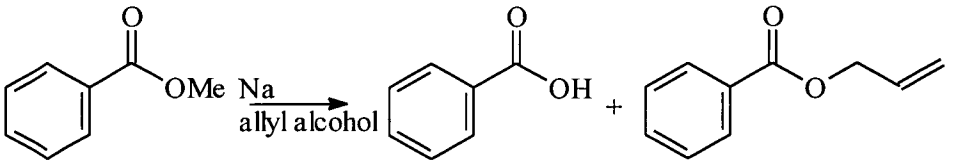
N(11) – C(21)	1.389 (4)
N(11) – C(131)	1.404 (4)
N(11) – C(141)	1.427 (4)
C(21) – C(31)	1.390 (4)
C(21) – C(71)	1.411 (4)
C(31) – C(41)	1.373 (5)
C(41) – C(51)	1.403 (5)
C(51) – C(61)	1.378 (5)
C(61) – C(71)	1.400 (5)
C(71) – C(81)	1.437 (5)
C(81) – C(91)	1.402 (4)
C(81) – C(131)	1.406 (4)
C(91) – C(101)	1.378 (5)
C(101) – C(111)	1.398 (5)
C(111) – C(121)	1.383 (4)
C(121) – C(131)	1.380 (4)
C(141) – C(191)	1.386 (4)
C(141) – C(151)	1.401 (4)
C(151) – C(161)	1.387 (4)
C(151) – C(201)	1.514 (4)
C(161) – C(171)	1.385 (5)

Table 29 Bond Angles (degrees)

C(21) - N(11) - C(131)	108.8 (3)
C(21) - N(11) - C(141)	127.1 (3)
C(131) - N(11) - C(141)	124.0 (3)
N(11) - C(21) - C(31)	129.5 (3)
N(11) - C(21) - C(71)	108.6 (3)
C(31) - C(21) - C(71)	121.9 (3)
C(41) - C(31) - C(21)	117.6 (3)
C(31) - C(41) - C(51)	121.9 (3)
C(61) - C(51) - C(41)	120.2 (3)
C(51) - C(61) - C(71)	119.4 (3)
C(61) - C(71) - C(21)	118.9 (3)
C(61) - C(71) - C(81)	134.2 (3)
C(21) - C(71) - C(81)	106.9 (3)
C(91) - C(81) - C(131)	118.7 (3)
C(91) - C(81) - C(71)	133.8 (3)
C(131) - C(81) - C(71)	107.6 (3)
C(101) - C(91) - C(81)	118.9 (3)
C(91) - C(101) - C(111)	120.8 (3)
C(121) - C(111) - C(101)	121.7 (3)
C(131) - C(121) - C(111)	117.0 (3)
C(121) - C(131) - N(11)	129.0 (3)

C(171) – C(181)	1.374 (5)	C(121) - C(131) - C(81)	122.9 (3)
C(181) – C(191)	1.385 (5)	N(11) - C(131) - C(81)	108.1 (3)
C(201) – O(211)	1.199 (4)	C(191) - C(141) - C(151)	120.3 (3)
C(201) – O(221)	1.320 (4)	C(191) - C(141) - N(11)	118.3 (3)
O(221) – C(231)	1.444 (4)	C(151) - C(141) - N(11)	121.4 (3)
		C(161) - C(151) - C(141)	118.6 (3)
		C(161) - C(151) - C(201)	119.5 (3)
		C(141) - C(151) - C(201)	122.0 (3)
		C(171) - C(161) - C(151)	121.0 (3)
		C(181) - C(171) - C(161)	119.9 (3)
		C(171) - C(181) - C(191)	120.3 (3)
		C(181) - C(191) - O(141)	119.9 (3)
		O(211) - C(201) - O(221)	125.3 (3)
		O(211) - C(201) - C(151)	124.0 (3)
		O(221) - C(201) - C(151)	110.7 (3)
		C(201) - O(221) - C(231)	114.6 (3)

Ester exchange reactions were then attempted using compound **401** as a substrate. Two sets of conditions were used, both involving compound **401** in allyl alcohol heated to reflux overnight. The first method used Hunig's base as a base, and the second used allyloxide as a base.[130] In each case, the ester exchange reaction was unsuccessful with recovery of unreacted starting materials. Therefore, a model study of ester exchange reactions was initiated using methyl benzoate **404** as a substrate. Methyl benzoate **404** was subjected to ester exchange conditions (allyloxide, allyl alcohol, heat), and was found to produce compounds **405** and **406** in a 4:1 ratio, as shown in **Scheme 160**.



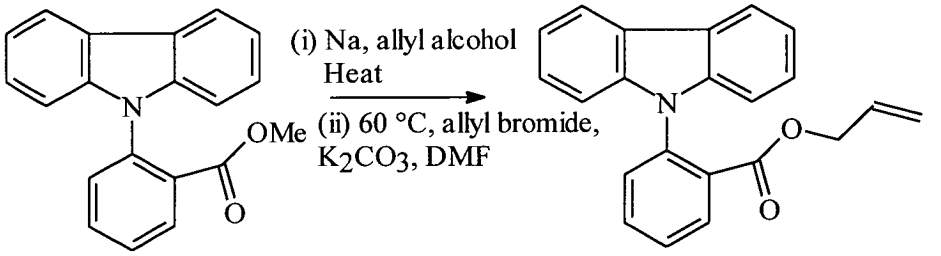
404 **405** **406**

Scheme 160

The presence of benzoic acid **405** as the major reaction product, suggested that hydrolysis was the predominant course of this reaction under these conditions. However, when this reaction was repeated using dry allyl alcohol, it resulted in the same ratio of products **405** and **406** which suggests that the ester may undergo an alkyl-oxygen bond fission to form the carboxylate anion. This would result in the

formation of the acid. The presence of the acid suggested that a second allylation step was required to obtain the allyl ester in a high yield.

Therefore, compound **401** was subjected to a one pot; two step process, which initially involved the deprotection of the methyl ester, then *in situ* esterification of the acid produced, using allyl bromide. However, initial esterification attempts at room temperature failed to give compound **407**. It was found that this allylation reaction had to be heated to 60 °C overnight in order to yield compound **407**. This was attributed to the steric factors. Compound **407** was finally obtained in 80% yield, as shown in **Scheme 161**.

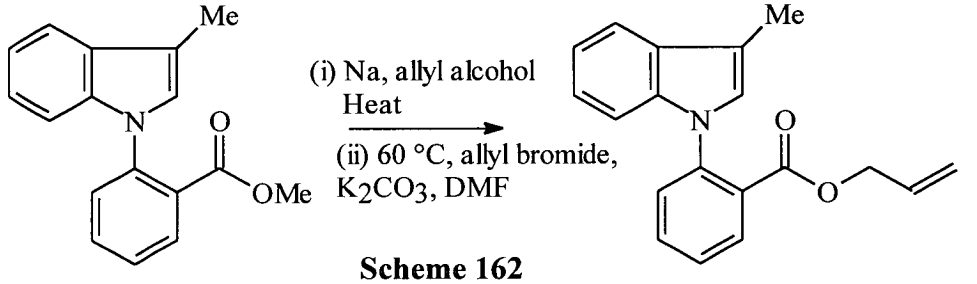


401 **407**

Scheme 161

5.3.2 2-Methylindole and 3-Methylindole analogues.

Similar conditions as described for the synthesis of compound **407** were used for the synthesis of compound **409** which was obtained in 77% yield, as shown in **Scheme 162**.



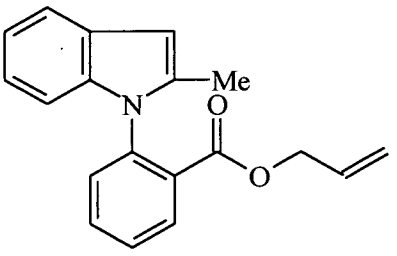
408 **409**

Scheme 162

The structure of compound **408** was confirmed by X-ray crystallography and is shown in **Figures 39** and **40** with the associated data in **Tables 30** and **31**. This structure is discussed in **Section 5.4**.

However, these conditions were unsuccessful for the synthesis of compound **410**. The initial *N*-arylation reaction using the methyl ester **403** was unsuccessful.

This was attributed to increased steric bulk at the *N*-arylation site due to the methyl group.



410

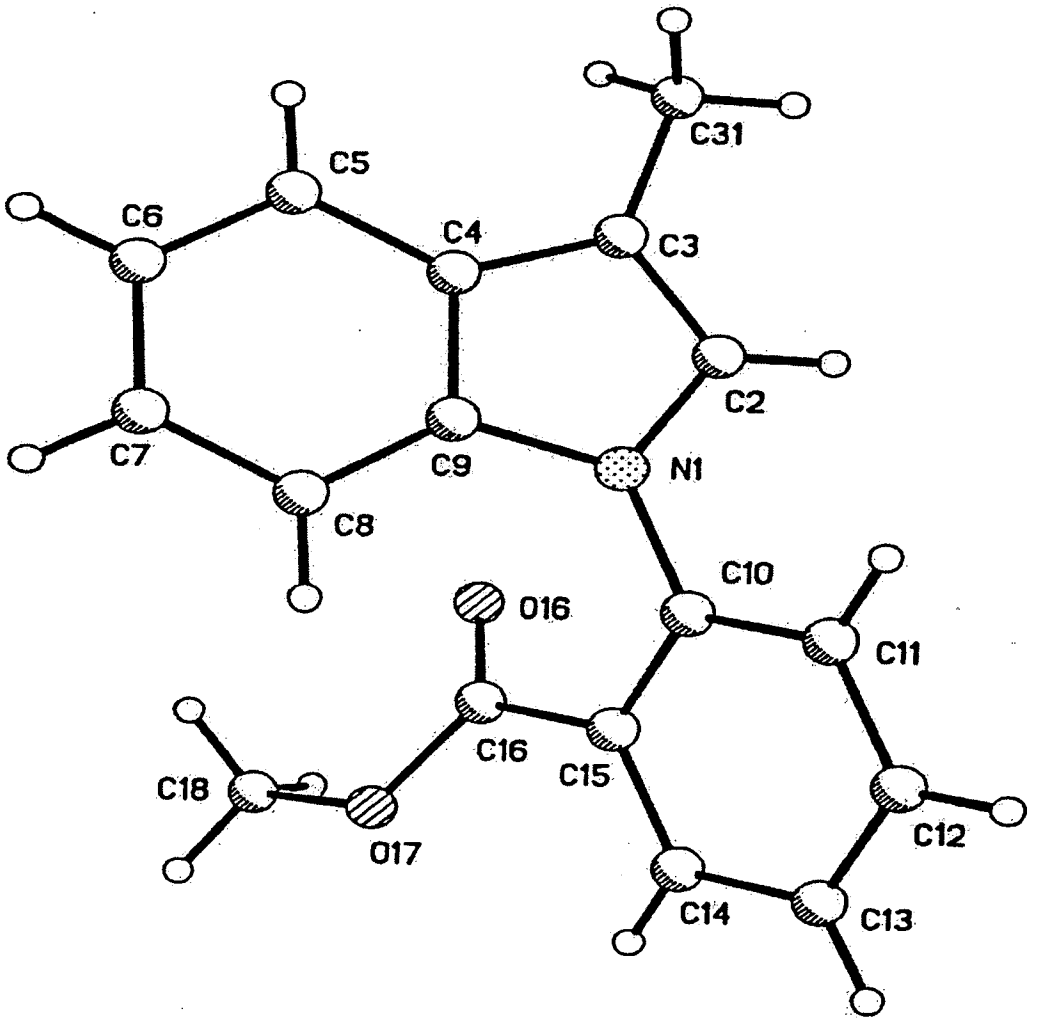


Figure 39

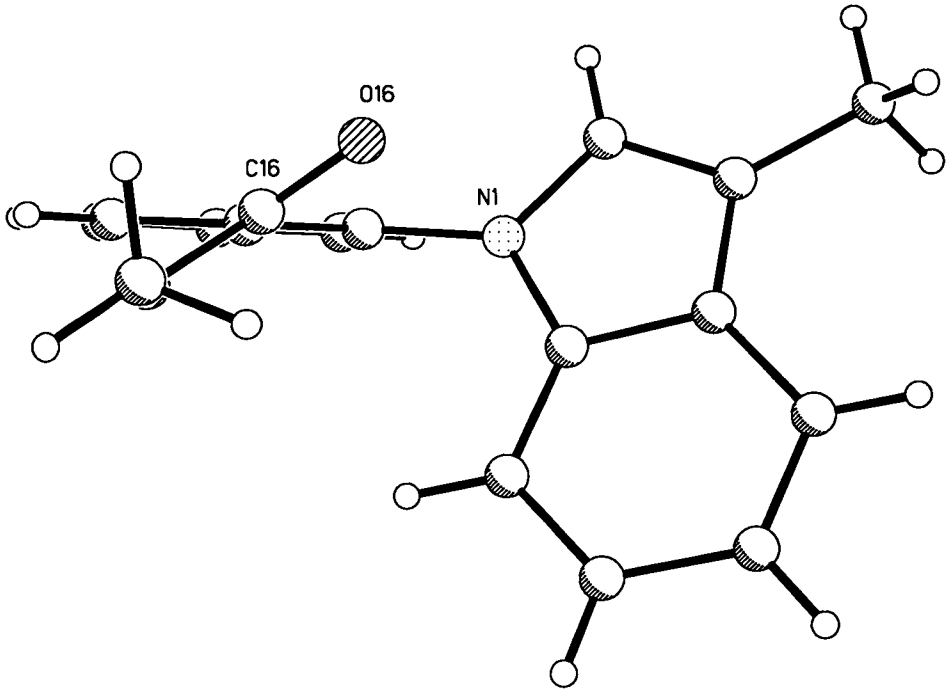


Figure 40

Table 30 Bond Lengths (Å)

N(1) – C(2)	1.385 (2)
N(1) – C(9)	1.3899 (17)
N(1) – C(10)	1.4251 (17)
C(2) – C(3)	1.362 (3)
C(3) – C(4)	1.419 (3)
C(3) – C(31)	1.495 (2)
C(4) – C(9)	1.396 (2)
C(4) – C(5)	1.423 (3)
C(5) – C(6)	1.385 (3)
C(6) – C(7)	1.396 (3)
C(7) – C(8)	1.380 (3)
C(8) – C(9)	1.394 (3)
C(10) – C11()	1.388 (2)
C(10) – C(15)	1.398 (3)
C(11) – C(12)	1.380 (3)
C(12) – C(13)	1.384 (2)
C(13) – C(14)	1.381 (3)
C(14) – C(15)	1.386 (2)
C(15) – C(16)	1.514 (2)
O(16) – C(16)	1.2025 (14)
C(16) – C(15')	1.22 (2)
C(16) – O(17)	1.3376 (16)

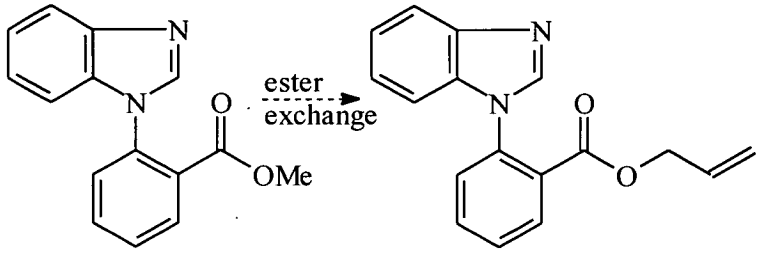
Table 31 Bond Angles (degrees)

C(2) – N(1) – C(9)	108.31 (12)
C(2) – N(1) – C(10)	125.22 (15)
C(9) – N(1) – C(10)	126.45 (14)
C(3) – C(2) – N(1)	110.32 (14)
C(2) – C(3) – C(4)	105.75 (14)
C(2) – C(3) – C(31)	126.94 (16)
C(4) – C(3) – C(31)	127.28 (16)
C(9) – C(4) – C(3)	109.29 (17)
C(9) – C(4) – C(5)	117.85 (19)
C(3) – C(4) – C(5)	132.86 (17)
C(6) – C(5) – C(4)	118.87 (16)
C(5) – C(6) – C(7)	121.09 (15)
C(8) – C(7) – C(6)	121.62 (17)
C(7) – C(8) – C(9)	116.91 (16)
N(1) – C(9) – C(8)	130.00 (14)
N(1) – C(9) – C(4)	106.33 (15)
C(8) – C(9) – C(4)	123.65 (16)
C(11) – C(10) – C(15)	119.24 (14)
C(11) – C(10) – N(1)	119.02 (14)
C(15) – C(10) – N(1)	121.67 (15)
C(12) – C(11) – C(10)	120.42 (16)
C(11) – C(12) – C(13)	120.2 (2)

O(17) – C(18)	1.4475 (16)	C(14) – C(13) – C(12)	119.9 (2)
N(1') – C(9')	1.351 (14)	C(13) – C(14) – C(15)	120.31 (17)
N(1') – C(2')	1.388 (16)	C(14) – C(15) – C(10)	119.88 (15)
N(1') – C(10')	1.454 (14)	C(14) – C(15) – C(16)	119.11 (18)
C(2') – C(3')	1.333 (17)	C(10) – C(15) – C(16)	120.83 (17)
C(3') – C(4')	1.422 (16)	O(16) – C(16) – C(15')	124.0 (18)
C(3') – C(31')	1.492 (17)	O(16) – C(16) – O(17)	123.88 (12)
C(4') – C(5')	1.370 (16)	C(15') – C(16) – O(17)	112.0 (18)
C(4') – C(9')	1.457 (15)	O(16) – C(16) – C(15)	125.06 (18)
C(5') – C(6')	1.402 (16)	C(15') – C(16) – C(15)	1 (2)
C(6') – C(7')	1.410 (16)	O(17) – C(16) – C(15)	111.04 (17)
C(7') – C(8')	1.381 (17)	C(16) – O(17) – C(18)	115.89 (11)
C(8') – C(9')	1.350 (17)	C(9') – N(1') – C(2')	102.2 (14)
C(10') – C(11')	1.366 (16)	C(9') – N(1') – C(10')	134.1 (15)
C(10') – C(15')	1.412 (217)	C(2') – N(1') – C(10')	123.7 (14)
C(11') – C(12')	1.381 (18)	C(3') – C(2') – N(1')	115.2 (16)
C(12') – C(13')	1.394 (18)	C(2') – C(3') – C(4')	106.5 (14)
C(13') – C(14')	1.364 (18)	C(2') – C(3') – C(31')	136 (2)
C(14') – C(15')	1.387 (18)	C(4') – C(3') – C(31')	117.4 (19)
		C(5') – C(4') – C(3')	143.8 (15)
		C(5') – C(4') – C(9')	113.3 (14)
		C(3') – C(4') – C(9')	102.6 (12)
		C(4') – C(5') – C(6')	127.3 (17)
		C(5') – C(6') – C(7')	114.6 (16)
		C(8') – C(7') – C(6')	121.6 (17)
		C(9') – C(8') – C(7')	120.6 (19)
		C(8') – C(9') – N(1')	124.6 (16)
		C(8') – C(9') – C(4')	121.8 (15)
		N(1') – C(9') – C(4')	112.8 (13)
		C(11') – C(10') – C(15')	124.7 (17)
		C(11') – C(10') – N(1')	117.9 (16)
		C(15') – C(10') – N(1')	116.8 (16)
		C(10') – C(11') – C(12')	121 (2)
		C(11') – C(12') – C(13')	116 (2)
		C(14') – C(13') – C(12')	119 (2)
		C(13') – C(14') – C(15')	128 (2)
		C(16) – C(15') – C(14')	126 (2)
		C(16) – C(15') – C(10')	124 (2)
		C(14') – C(15') – C(10')	106.6 (19)

5.3.3 Benzimidazole Analogue.

It was anticipated that a similar strategy could be adopted for the synthesis of compound **412**, as shown in **Scheme 163**.

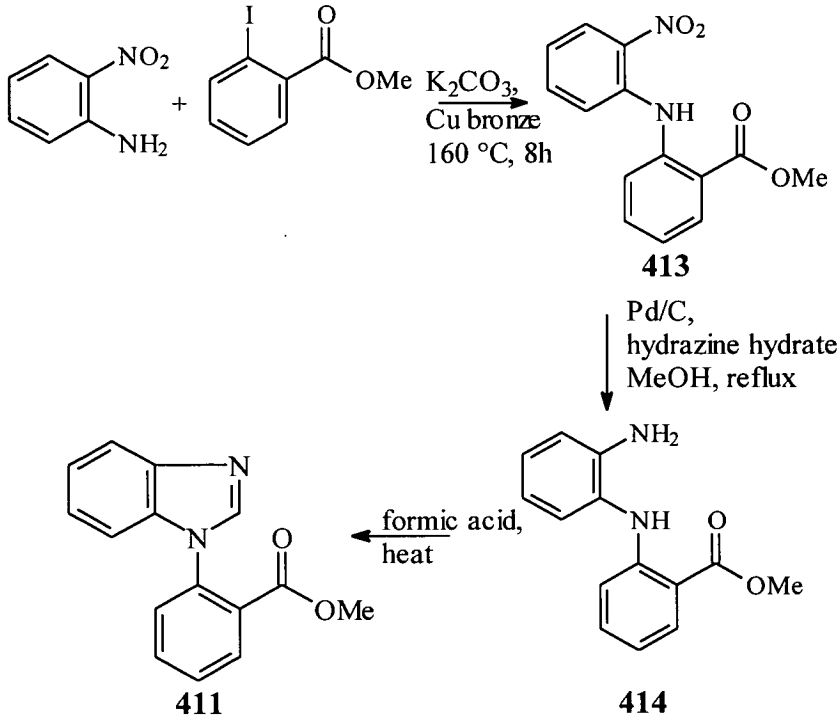


411 **412**

Scheme 163

The methyl ester **411** is a known compound, and this literature method[131, 132] was adopted for its synthesis and is shown in **Scheme 164**.

This 3-step method involved the coupling of *o*-nitroaniline and methyl ester **403** to form compound **413** which occurred in 75% yield. Compound **413** was reduced to compound **414** in 90% yield. Finally, compound **411** was formed from compound **414** in 60% yield.



411 **413** **414**

Scheme 164

Although the mass spectrum of the product showed the molecular ion at *m/z* 252, as expected for **411**, and the melting point agreed with the literature value,[132] the ^{1}H and ^{13}C NMR spectra proved to be unusual. The ^{1}H and ^{13}C NMR spectra for compound **411** are shown in **Figures 41** and **42** respectively. The proton spectrum shows broad signals between 7.1 - 7.4 ppm and 7.8 - 8.0 ppm which would not be expected from the C-H signals in product **411**. This was not observed in the carbazole or indole analogues. This broadening was observed when the proton spectrum was run in [^{2}H]DMSO and [^{2}H]chloroform suggesting that this effect was not due to the NMR solvent.

This compound was therefore subjected to ^{1}H NMR spectroscopy at higher and lower temperatures. The higher temperature spectra are shown in **Figures 41a, 41b** and **41c** and these show that the broadened signals sharpen as the temperature of the NMR experiment increases. The lower temperature NMR spectra of compound **411** are shown in **Figures 41d** and **41e** and these also show a sharpening of the broadened signals as the temperature is decreased.

It is unusual for broadened peaks on a proton spectrum to sharpen at both lower and higher temperatures. This suggests that there is exchange between two identical sites resulting in identical spectra at both increased and decreased temperatures.

The carbon spectrum for compound **411** is also unusual as there are 3 quaternaries and a C-H signal missing and there is a broad peak at ~142 ppm. This is attributed

In view of the unusual spectroscopic behaviour, the structure of compound **411** was confirmed by X-ray crystallography and is shown **Figures 43** and **44**, with the associated data in **Tables 32** and **33**.

^{1}H NMR spectrum of compound **411**.

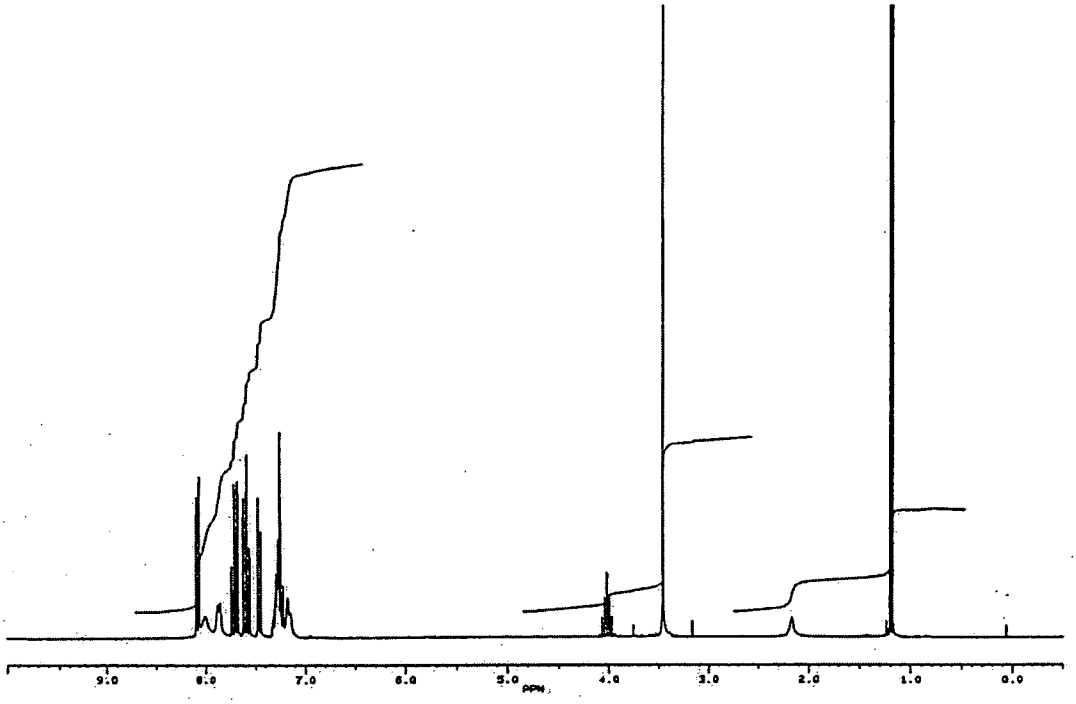


Figure 41

^{13}C NMR spectrum of compound **411**.

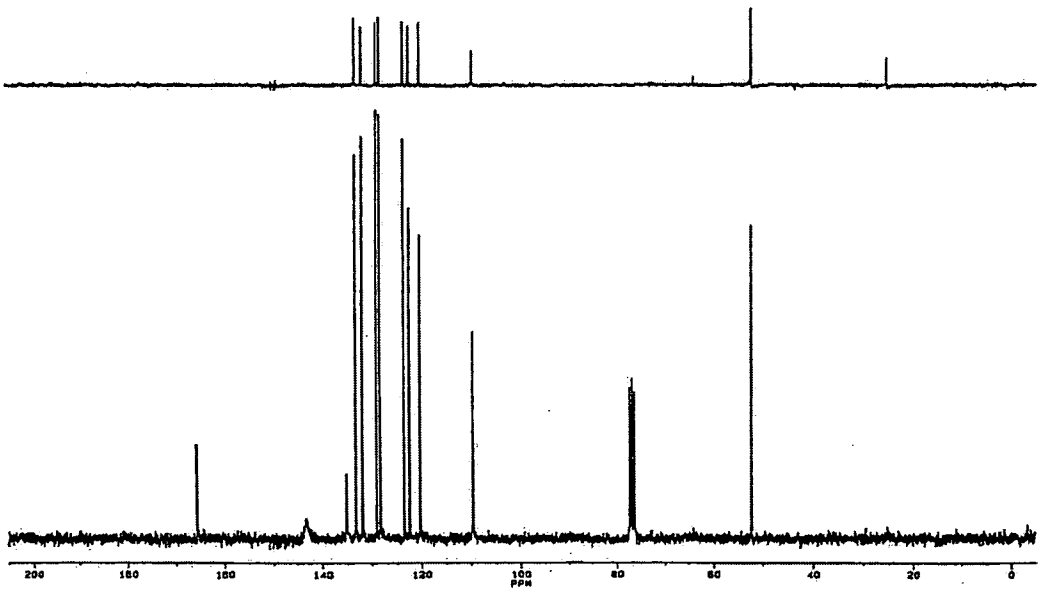


Figure 42

Variable Temperature NMR for compound **411**.

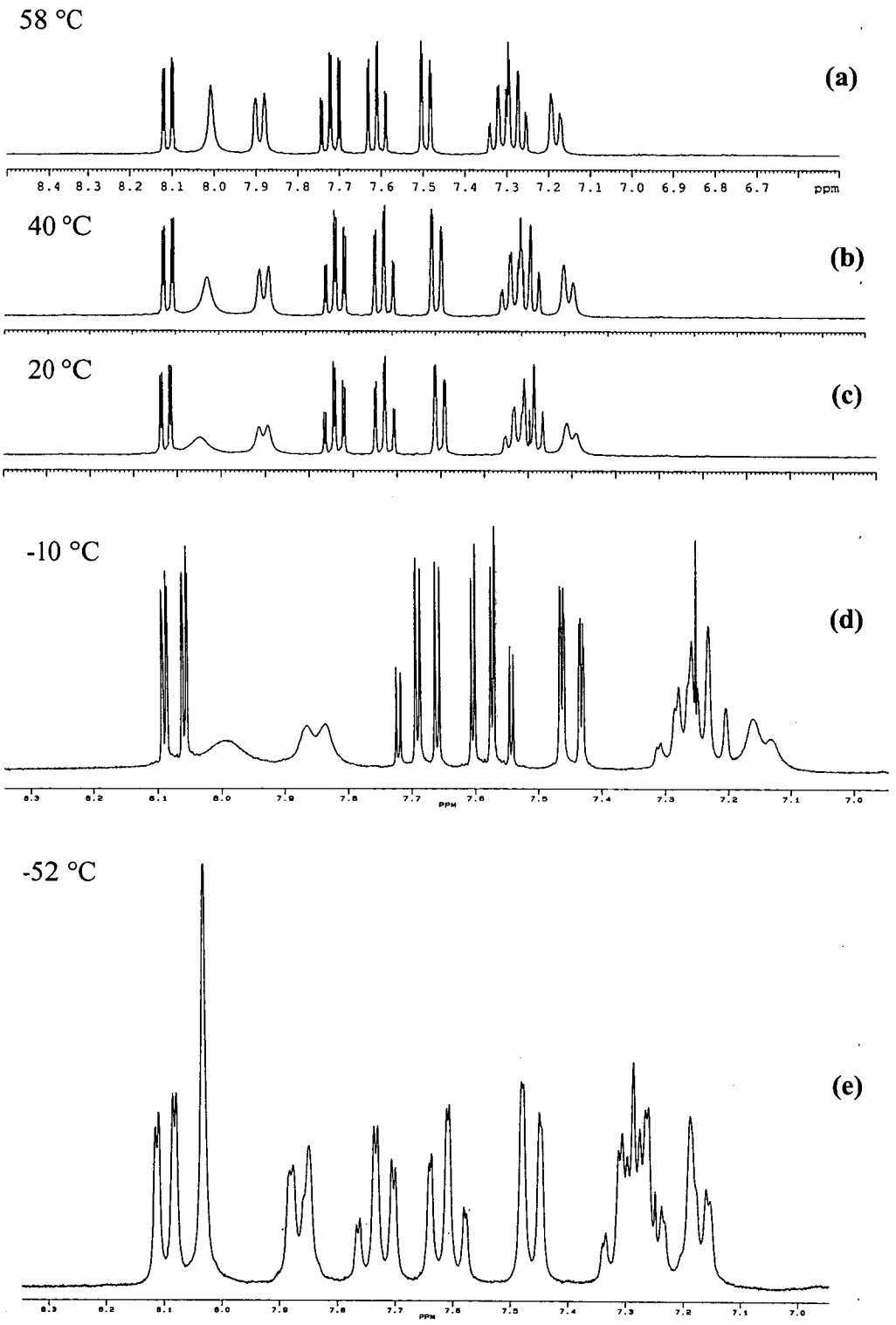


Figure 41

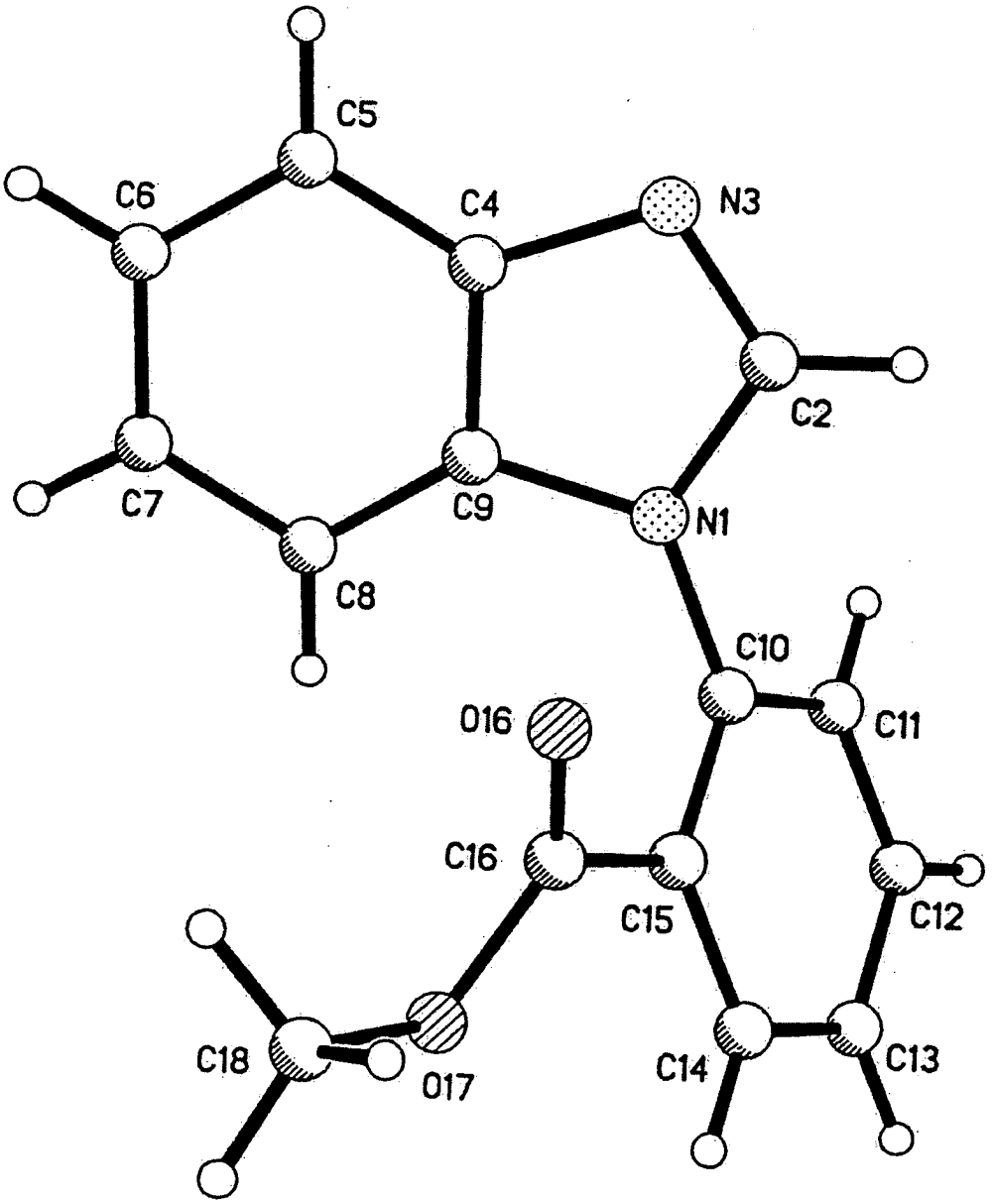


Figure 43

C(10) - C(15) - C(16)	121.56 (11)
O(16) - C(16) - O(17)	123.74 (11)
O(16) - C(16) - C(15)	125.03 (11)
O(17) - C(16) - C(15)	111.21 (10)
C(16) - O(17) - C(18)	116.05 (10)

However, attempts to synthesise allyl ester **412** using the same deprotection-reesterification method used as for the synthesis of compounds **407** and **409**, proved to be unsuccessful. This strategy was abandoned when a more convenient method was developed. (see **Section E**)

5.4 Crystal Structures.

There are no significant differences in the bond lengths around the *N*-aryl group, or the ester group in compounds **401**, **411** and **408**. There are also no significant differences in the bond angles. The angles between the plane of the heterocycle (carbazole, 3-methylindole or benzimidazole), the plane of the benzene ring substituted on the nitrogen atom, and the plane of the ester group were obtained and are shown in **Table 34**.

Compound	Angle between heterocycle plane and *N*-aryl plane.	Angle between *N*-aryl plane and nitro group plane
401	65.79(8)	33.80(12)
411	63.60(3)	34.49(3)
408	64.93(8)	37.13(6)

Table 34:- Angles between the planes of compounds **401**, **411** and **408**.

The angles between the planes shown in **Table 34** are fairly constant for compounds **401**, **408** and **411**. It should be noted that the ester group has been distorted out of the plane by a significant angle. This is shown in **Figures 38**, **40** and **44**. This non-planarity is caused by a major steric interaction with the aryl group of the heterocycle.

5.5 Pyrolysis of allyl esters.

Compound **409** was pyrolysed at 950 °C and resulted in compound **400** in 28% yield, as shown in **Scheme 165**.

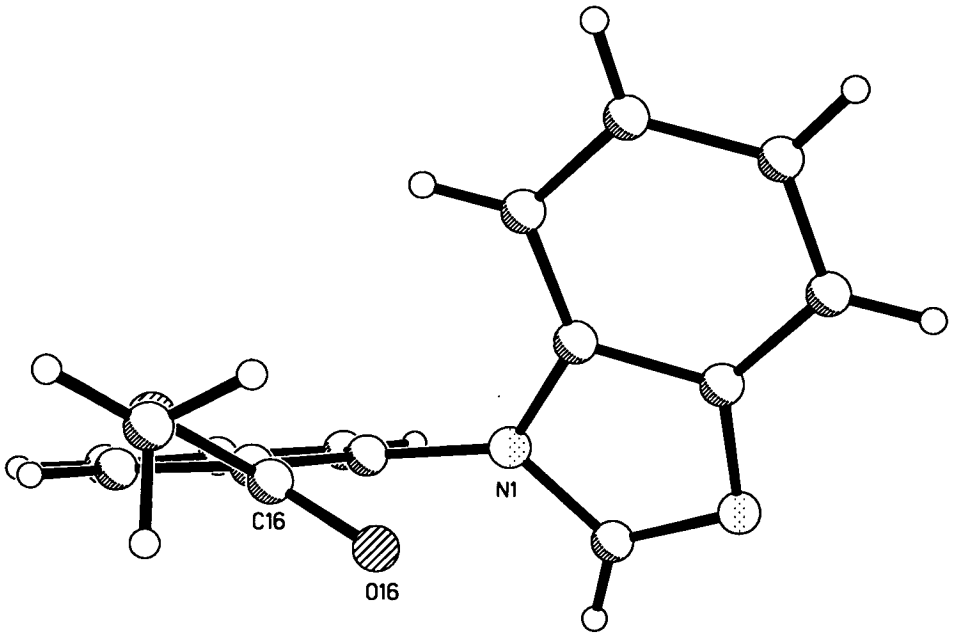


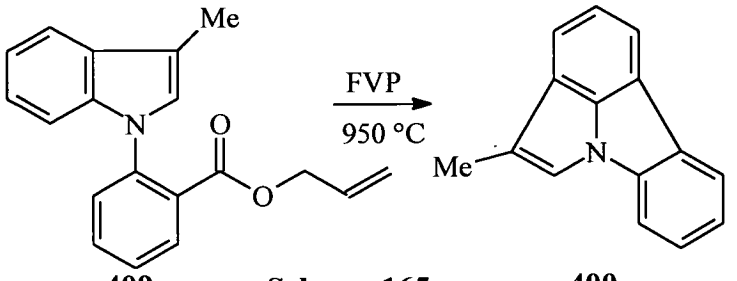
Figure 44

Table 32 Bond Lengths (Å)

N(1) - C(2)	1.3678 (15)
N(1) - C(9)	1.3882 (15)
N(1) - C(10)	1.4282 (15)
C(2) - N(3)	1.3050 (16)
N(3) - C(4)	1.3940 (17)
C(4) - C(5)	1.3953 (18)
C(4) - C(9)	1.3963 (16)
C(5) - C(6)	1.3746 (19)
C(6) - C(7)	1.3993 (18)
C(7) - C(8)	1.3789 (18)
C(8) - C(9)	1.3868 (18)
C(10) - C(11)	1.3851 (16)
C(10) - C(15)	1.4022 (17)
C(11) - C(12)	1.3821 (18)
C(12) - C(13)	1.3825 (19)
C(13) - C(14)	1.3796 (17)
C(14) - C(15)	1.3893 (17)
C(15) - C(16)	1.4890 (17)
O(16) - C(16)	1.2049 (14)
C(16) - O(17)	1.3399 (15)
O(17) - C(18)	1.4450 (15)

Table 33 Bond Angles (degrees)

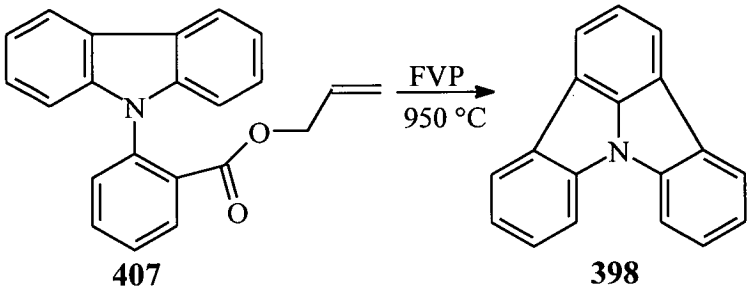
C(2) - N(1) - C(9)	105.95 (10)
C(2) - N(1) - C(10)	126.49 (11)
C(9) - N(1) - C(10)	127.53 (10)
N(3) - C(2) - N(1)	114.32 (12)
C(2) - N(3) - C(4)	104.14 (10)
N(3) - C(4) - C(5)	130.04 (12)
N(3) - C(4) - N(9)	110.42 (11)
C(5) - C(4) - C(9)	119.53 (12)
C(6) - C(5) - C(4)	118.04 (12)
C(5) - C(6) - C(7)	121.59 (13)
C(8) - C(7) - C(6)	121.32 (13)
C(7) - C(8) - C(9)	116.70 (12)
C(8) - C(9) - N(1)	132.00 (11)
C(8) - C(9) - C(4)	122.82 (11)
N(1) - C(9) - C(4)	105.16 (11)
C(11) - C(10) - C(15)	120.30 (11)
C(11) - C(10) - N(1)	118.61 (11)
C(15) - C(10) - N(1)	121.07 (10)
C(12) - C(11) - C(10)	120.03 (12)
C(11) - C(12) - C(13)	20.21 (12)
C(14) - C(13) - C(12)	119.86 (12)
C(13) - C(14) - C(15)	121.04 (12)
C(14) - C(15) - C(10)	118.53 (11)
C(14) - C(15) - C(16)	119.82 (11)



409 **Scheme 165** **400**

This is another example of the substituted pyrrolo[3,2,1-*jk*]carbazole system. These were discussed in **Section C**, where the parent system **361** was subjected to different conditions to produce substituted analogues. The route shown in **Scheme 165** describes an alternative method to such analogues, where a substituted pyrolysis precursor results in the substituted pyrrolo[3,2,1-*jk*]carbazole.

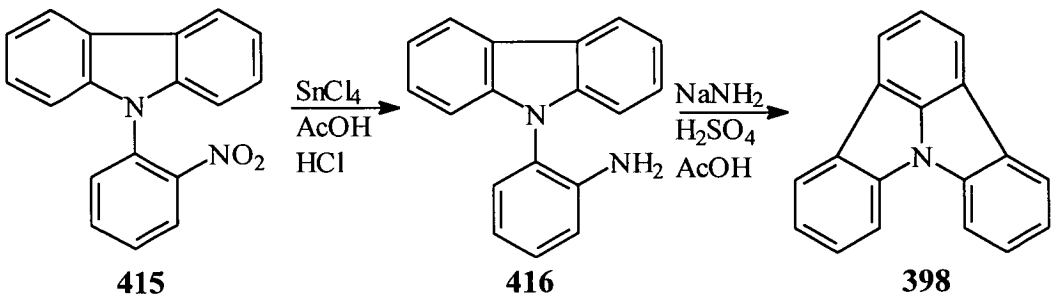
Compound **407** was subjected to pyrolysis conditions at 950 °C, and as expected, this produced indolo[3,2,1-*jk*]carbazole **398** in 60% yield, as shown in **Scheme 166.**



407 **398**

Scheme 166

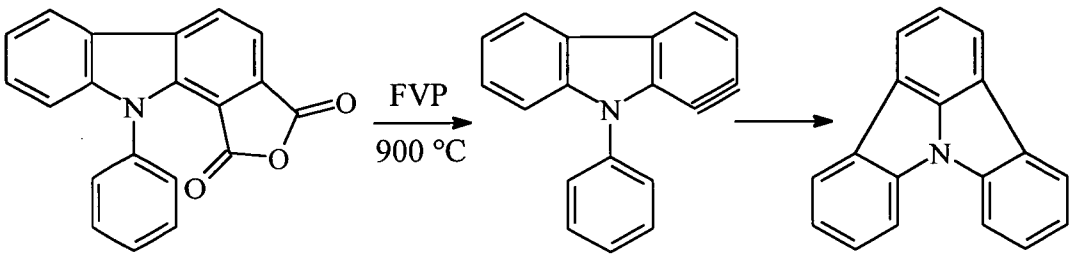
This compound was identified by comparison to literature spectra.[117] Compound **398** is a known compound, and has been synthesised by two methods. In the 1930's, Tucker and co-workers[133] reduced compound **415** to form compound **416** in 74% yield. This was reacted with nitrous acid *in situ*, and compound **398** was formed in 56% yield *via* the diazonium salt, as shown in **Scheme 167**.



415 **416** **398**

Scheme 167

Brown and co-workers[117] have also produced compound **398** *via* a FVP method, as shown in **Scheme 168**.



417 **398**

Scheme 168

Compound **417** was pyrolysed at 900 °C, and formed compound **398** in 83% yield.

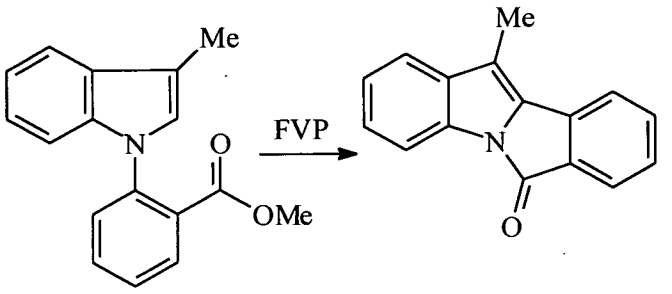
Compound **398** was also subjected to electrochemical experiments by Dr A.R. Mount and Miss M. Chapman. (see **Section C3.4.6**) When compound **398** was subjected to electro-oxidation in a stirred solution, a steady state current was observed. This was in contrast to the behaviour of compound **361**, and this was due to the formation of a conducting film which was redox active. This compound was also highly fluorescent. There are only a few examples of compounds which form conducting films in this way, *e.g.* pyrrole, indole and thiophene. Compound **398** represents a new class of compounds that act in this way and is currently being investigated.[134]

The pyrolysis of the allyl esters **394**, **407** and **409** all result in the expected compounds **361**, **398** and **400**. However, developing a robust synthesis for the synthesis of these allyl esters proved to be troublesome and therefore an alternative method for the generation of the phenyl radical intermediate was desired. This is discussed in **Section E**.

5.6 Pyrolysis of the Methyl esters.

As the synthesis of the allyl esters proved troublesome, the corresponding methyl esters were pyrolysed to see if they could give direct access to the desired compounds.

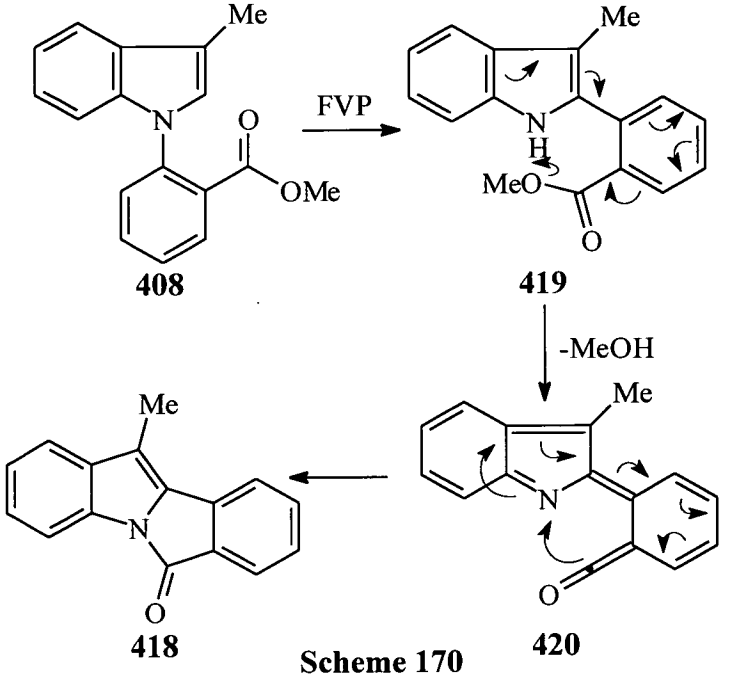
The pyrolysis of methyl ester **408** resulted in compound **418** in 43% yield, as shown in **Scheme 169**.



408 **418**

Scheme 169

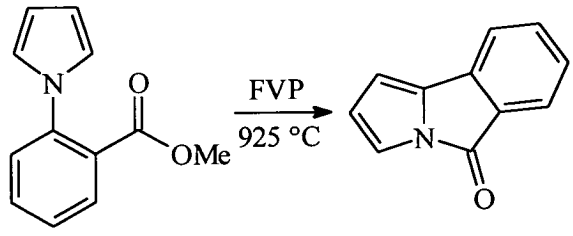
The mechanism for the formation of this product is shown in **Scheme 170**.



408 **419** **418** **420**

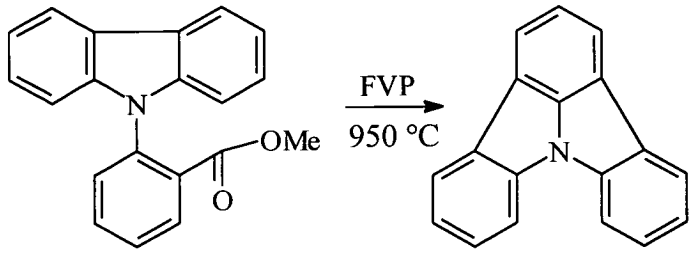
Scheme 170

Compound **408** undergoes a 1,5-aryl shift to give intermediate **419** which then eliminates methanol to give the ketene intermediate **420**. Intermediate **420** cyclises to the product **418**. This is not surprising as this type of mechanism has been proposed for the cyclisation of other 1-(2-methoxycarbonylphenyl) substituted heterocycles.[135] An example is shown in **Scheme 171** where compound **421** cyclises to compound **422** in 79% yield.



421 **Scheme 171** 422

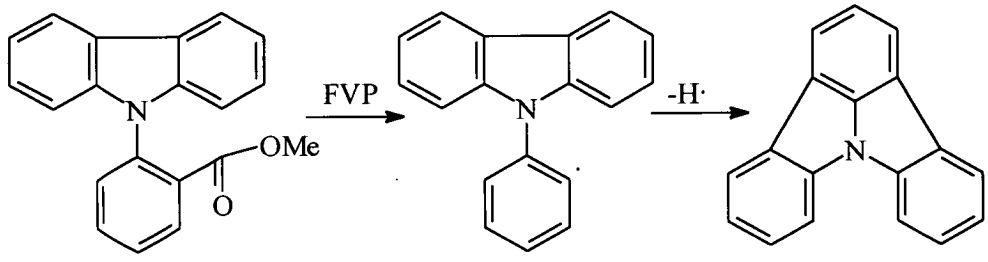
This was extended to the pyrolysis of compound **401** and resulted in compound **398** in 30% yield, as shown in **Scheme 172**. [Silica tubes were placed in the furnace, as without them recovered **401** was obtained in pyrolyses reactions at this temperature.] (Using silica tubes in the furnace tube has the equivalent effect on the pyrolysis of raising the furnace temperature by 50 °C. This is due to the increased contact time of the molecules in the hot zone.[136]).



401 **398**

Scheme 172

The pyrolysis of this ester is unusual, as the formation of compound **398** suggests that a radical mechanism is occurring, as shown in **Scheme 173**.



401 **423** **398**

Scheme 173

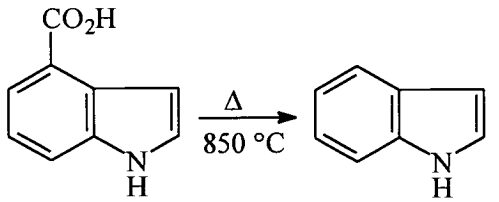
Compound **401** pyrolyses to give radical **423**, which cyclises with the loss of a hydrogen atom, to give compound **398**. The presence of the fused rings blocks the α-position, therefore the initial 1,5-aryl migration observed for compound **408** is disfavoured. It should be noted that the yield for compound **398** using the methyl

ester precursor **401** is 30%, which is much less than the 60% yield obtained from the pyrolysis of the allyl ester precursor **407**. Further work by McNab and co-workers[137] has shown that the initial 1,5-aryl shift in the pyrolysis of compounds such as **421**, will follow an unsubstituted pathway and be stopped if there is any substitution.

5.7 Mechanism for the Decarboxylation of Carboxylic Acids.

There are several literature references[138, 139] to the gas-phase decarboxylation of carboxylic acids. However, the mechanism for this reaction has not been fully investigated.

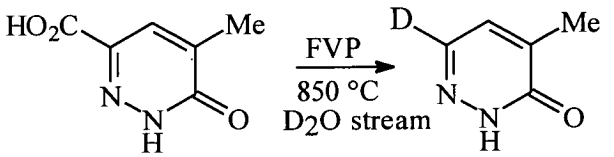
Work by Brown and co-workers[138] has described the decarboxylation of compound **424** to compound **395** in 65% yield, as shown in **Scheme 174**. This process was not optimised, and no mechanistic details of this reaction were reported.



424 **395**

Scheme 174

This work was extended by McNab,[139] who has described the synthesis of compound **426** by the pyrolysis of compound **425** in a D_2O stream, as shown in **Scheme 175**.

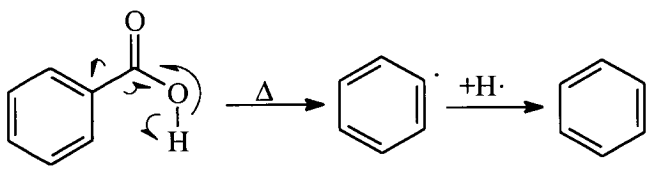


425 **426**

Scheme 175

However, no details of the reaction were reported.

There are several possible mechanisms for such decarboxylation processes. A radical mechanism is shown in **Scheme 176**.

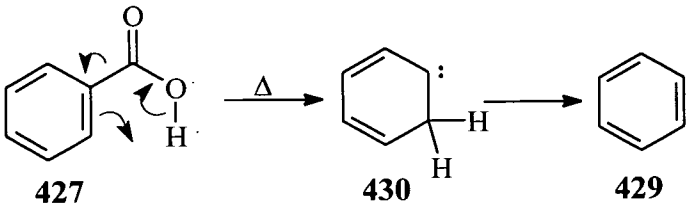


427 **428** **429**

Scheme 176

Acid **427** loses carbon dioxide and a hydrogen atom to form radical **428**, which then picks up a hydrogen atom to give product **429**.

A second mechanism for this reaction is shown in **Scheme 177**.

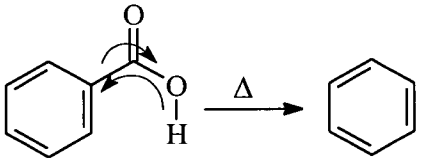


427 **430** **429**

Scheme 177

In this case, acid **427** loses carbon dioxide to form carbene **430** which then inserts into the adjacent CH_2 group to give product **429**.

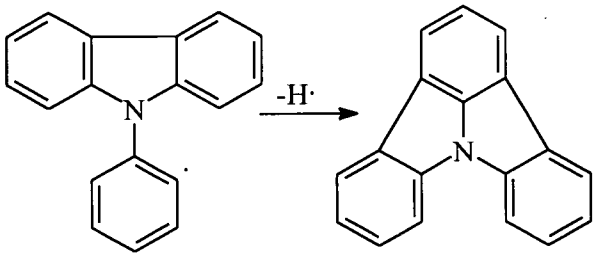
A 4-centre mechanism is shown in **Scheme 178**, where compound **427** loses carbon dioxide to give compound **429** with the hydrogen of the acid specifically taking the place of the acid.



427 **429**

Scheme 178

From the pyrolysis of compound **408**, it is known that if radical **423** is formed, this will cyclise to give compound **398**, as shown in **Scheme 179**.

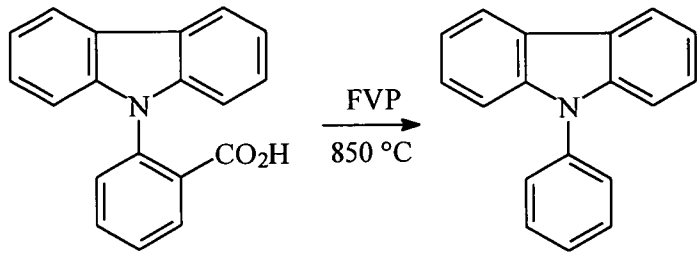


423 **398**

Scheme 179

Therefore, if the corresponding carboxylic acid was pyrolysed, and the decarboxylation occurs by a radical mechanism, then compound **398** would be the only expected product.

Compound **431** was obtained in low yield, by the hydrolysis of compound **401**. Compound **431** was pyrolysed at 850 °C, and produced compound **432** exclusively in 33% yield, as shown in **Scheme 180**.

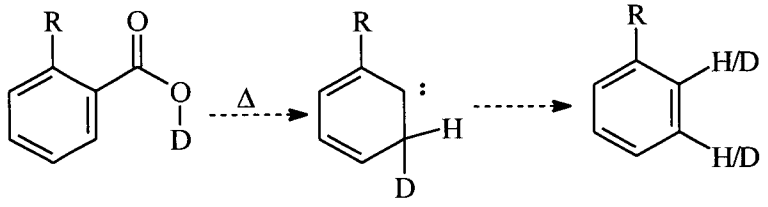


431 **432**

Scheme 180

This result suggested that the decarboxylation reaction does not occur by a radical mechanism.

It was thought that deuterium labelling experiments could be used to confirm the second mechanism, as shown in **Scheme 181**.

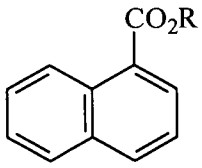


433 **434** **435**

Scheme 181

If compound **433** was pyrolysed, then the deuterium atom would be incorporated in intermediate **434**. Product **435** would contain deuterium in the 2- and 3-positions.

1-Naphthoic acid **436a** was chosen as a suitable precursor, as the proton signals for the 1- and 2-protons occur in distinct chemical shifts (that are far enough away from each other). Therefore a deuterium signal could be unambiguously identified for each of these positions in a deuterium NMR experiment.



a; R = H
b; R = D

436

However, when compound **436b** was pyrolysed at 950 °C, the deuterium NMR spectrum showed no signals, due to deuterium incorporation. These results suggest

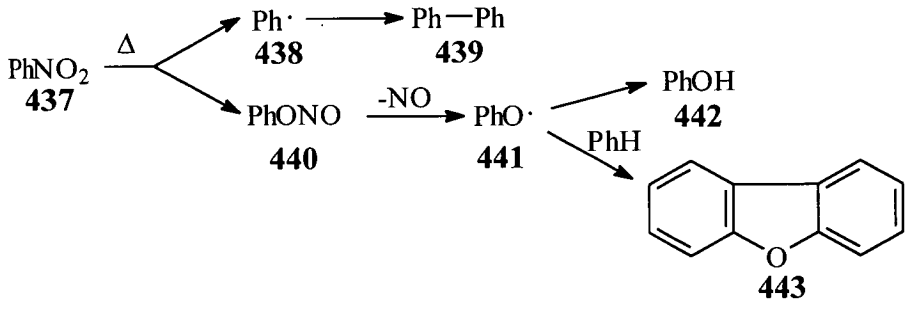
that the gas phase decarboxylation process does not follow a radical mechanism, but the actual mechanism has not been fully elucidated.

E. The use of the Nitro Group as an Aryl Radical Generator.

6.1 Preamble

The difficulties associated with the synthesis of the allyl ester compounds, described in **Section D**, made the use of an alternative phenyl radical generator an attractive extension to this work. A strong electron withdrawing group, which would make the initial *N*-arylation reactions much easier, and which could then either be used as an aryl radical generator, or be converted to an aryl radical generator, was desired. The strong electron withdrawing character of the nitro group made it an obvious choice. However, the literature on the pyrolysis behaviour of aryl nitro groups proved to be contradictory.

Fields and Meyerson[140, 141] have described the atmospheric pressure flow pyrolysis reactions of some aromatic nitro compounds. An example is shown in **Scheme 182**.

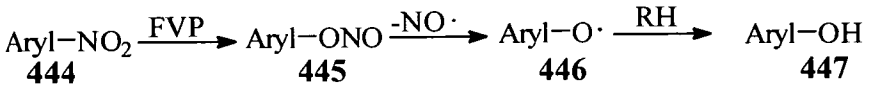


Scheme 182

Compound **437**, when pyrolysed at 600 °C, can take several different pathways. In the first pathway, the phenyl radical **438** is produced which can dimerise to give compound **439** in 20% yield. In the second pathway, compound **437** rearranges to give **440** which then loses NO to give phenoxy radical **441**. This can pick up a hydrogen atom[90] to give the phenol **442** in 27% yield. The phenoxy radical **441** can also be further reacted with benzene, which can eventually result in dibenzofuran **443** in 15% yield.

This work suggests that the flow pyrolysis reactions of aromatic nitro compounds are complex. These compounds are a source of aryl radicals but this process is in competition with rearrangements which can form the major products from the pyrolysis.

More recently, Wiersum[142] has reported that compounds **444a**, **444b** and **444c** form compounds **447a**, **447b** and **447c** in fair yields, when subjected to flash vacuum pyrolysis reactions between 750 - 800 °C. as shown in **Scheme 183**.

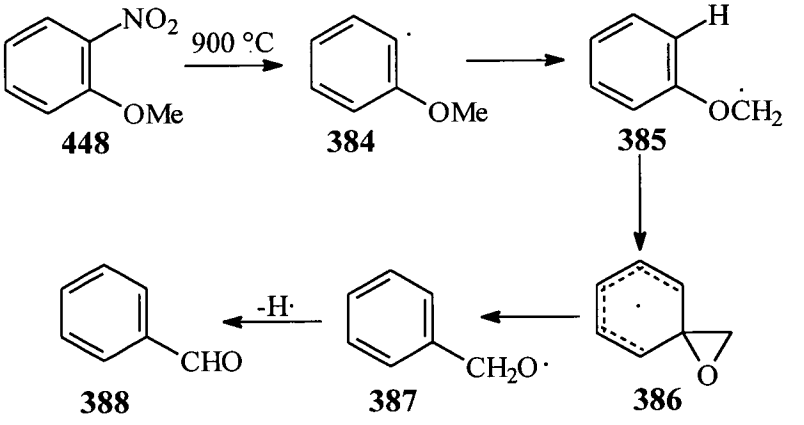


Aryl = **a**; 1-pyrenyl
b; 3-fluoranthyl
c; 6-chrysenyl

Scheme 183

It is thought that compound **444** equilibrates to the nitrite esters **445** which lose NO and form the aryloxy radical **446**. These radicals will pick up hydrogen to form the hydroxy compounds **447**. This hydrogen abstraction has been observed previously.[90]

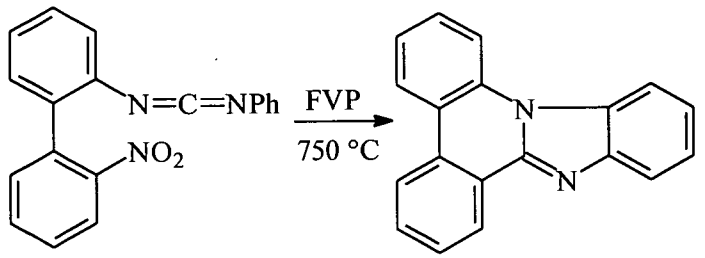
However, work by DeMayo and co-workers[89] suggests that the pyrolysis of compound **448** resulted in benzaldehyde **388** *via* the phenyl radical **384**, as shown in **Scheme 184**.



Scheme 184

Compound **448** pyrolyses to form phenyl radical **384**, which then rearranges to form radical **385**. This forms the three membered ring as in intermediate **386** which opens in the opposite sense to form radical **387**. The loss of a hydrogen atom forms benzaldehyde **388**.

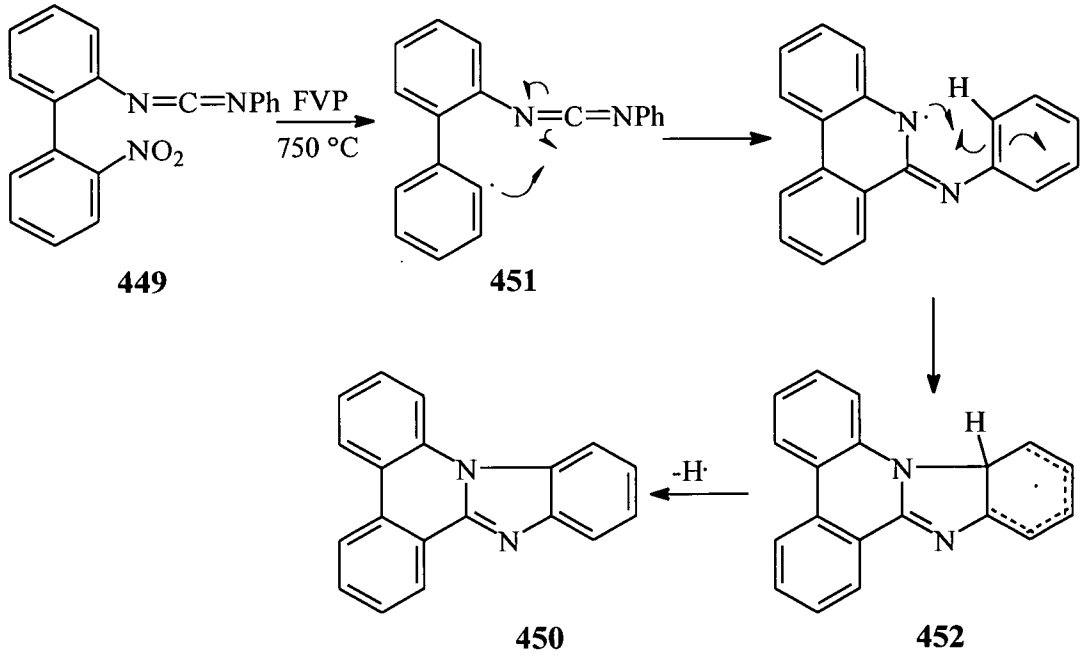
Rees and co-workers[143, 144] have reported that the pyrolysis of compound **449** at 750 °C gives compound **450**, as shown in **Scheme 185**.



449 **450**

Scheme 185

Although the authors suggest a dipolar mechanism for this reaction, the work by DeMayo suggests that a radical mechanism is most likely. A proposed radical mechanism is shown in **Scheme 186**.



449 **451** **450** **452**

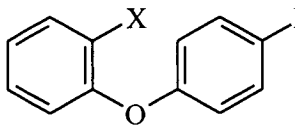
Scheme 186

The carbodiimide **449** loses the nitro group on pyrolysis to form the phenyl radical **451**. This cyclises to form radical **452** which loses a hydrogen atom to form product **450**.

The results reported by Wiersum,[142] Fields and Meyerson[140, 141] suggest that the pyrolysis reactions of aromatic nitro compounds are messy, with different competing reaction pathways, and phenols in particular, are prominent products. The work by Rees[143, 144] and DeMayo[89] suggests that an aryl radical is formed which undergoes different rearrangements.

6.2 Synthesis and Pyrolysis of Nitrophenyl Ethers.

Due to the contradictory nature of this literature, a model reaction was designed. A compound whose radical behaviour was known and where the corresponding nitro compound could be synthesised easily, was required so that the pyrolysis behaviour of these aromatic nitro compounds could be clarified.

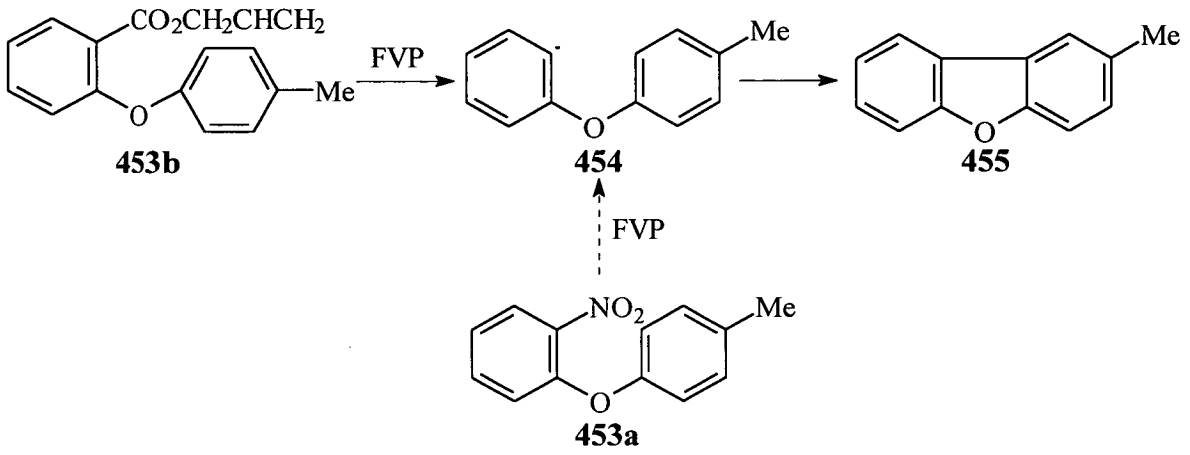


453

a; $X=NO_2$

b; $X=CO_2CH_2CHCH_2$

Compound **453a** was chosen as a suitable precursor, as the pyrolysis of the corresponding allyl ester **453b** is a literature reaction,[126] and it is known to give radical **454** which cyclises to give 2-methyldibenzofuran **455**. It was hoped that the pyrolysis of the nitro compound **453a** would yield the same product, *via* the same phenyl radical as shown in **Scheme 187**.



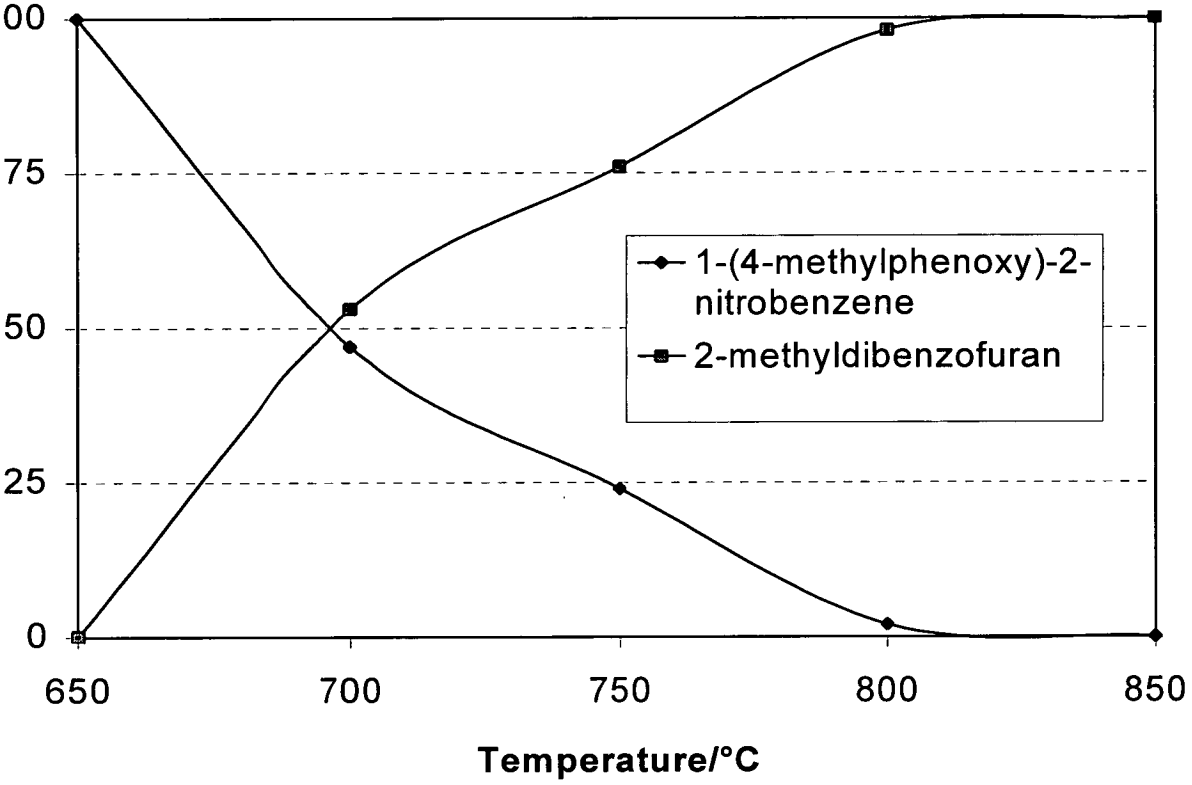
453b **454** **455** **453a**

Scheme 187

The nitro compound **453a** was synthesised using a literature method, from *o*-chloronitrobenzene and *p*-cresol in 63% yield and subjected to flash vacuum pyrolysis at a range of temperatures from 650 – 750 °C. These pyrolyses showed the presence of recovered starting material **453a** and the expected 2-methyldibenzofuran **455** with no other products present. The "clean" nature of this reaction is in direct contrast to the results of the pyrolysis reactions that Wiersum, Fields and Meyerson have reported. It should also be noted that there was no trace of the hydroxy compound, which again was in contrast to some of the literature. The percentage

conversion of 1-(4-methylphenoxy)-2-nitrobenzene to 2-methyldibenzofuran is shown in **Graph 3**.

Graph 3-Temperature dependence of pyrolysis of 1-(4-methylphenoxy)-2-nitrobenzene.



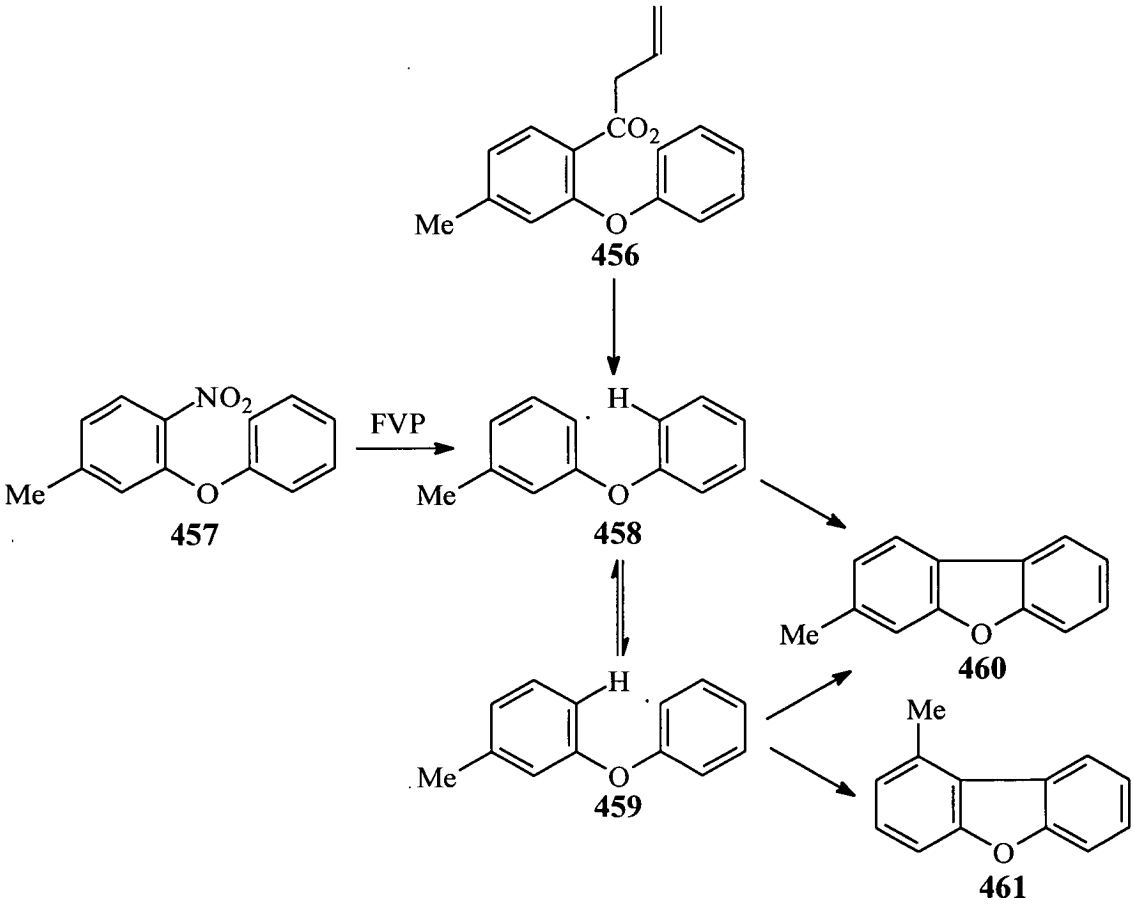
This graph shows that a pyrolysis temperature of 850 °C is required for complete conversion of 1-(4-methylphenoxy)-2-nitrobenzene to 2-methyldibenzofuran, and is therefore the optimum pyrolysis temperature for these nitro compounds.

However, although this reaction suggested that phenyl radical **454** was an intermediate in the reaction, a further experiment was carried out to confirm that the pyrolysis pathway of an aryl nitro compound follows a radical mechanism.

The allyl ester **456** is known to generate radical **458**, under FVP conditions.[145] This can cyclise directly to give 3-methyldibenzofuran **460**, or equilibrate to radical **459** which can in turn cyclise to give either

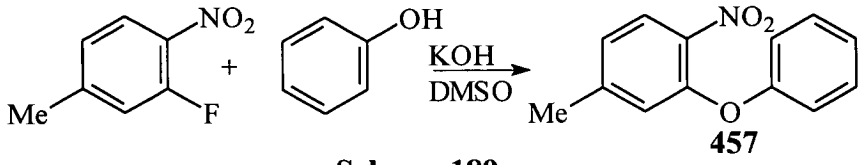
3-methyldibenzofuran **460** or 1-methyldibenzofuran **461**. These products (**460** and **461**) were produced in a statistical ratio of 3:1.

It was anticipated that if the corresponding nitro compound **457** was pyrolysed and resulted in these two compounds **460** and **461** in a 3:1 ratio, the reaction must proceed *via* radical **458**, confirming the mechanism. This is illustrated in **Scheme 188**.



Scheme 188

Compound **457** was synthesised from phenol and 3-fluoro-4-nitrotoluene, as shown in **Scheme 189**, in 59% yield.

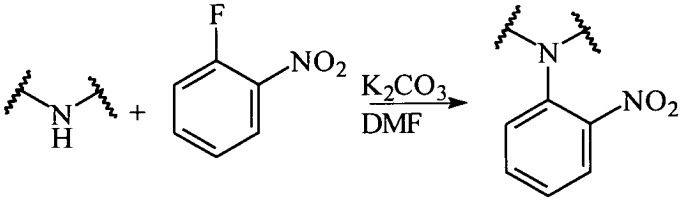


Scheme 189

When compound **457** was pyrolysed at 850 °C, compounds **460** and **461** were produced in a 3:1 ratio confirming that the mechanism for this reaction must involve phenyl radical **458**.

6.3 Synthesis of 1-(2-nitrophenyl) substituted heterocycles.

A variety of heterocycles was subjected to the literature *N*-arylation conditions of heating in DMF at 125 °C, with potassium carbonate and *o*-fluoronitrobenzene. This was a literature method for the *N*-arylation of benzimidazole which was extended to the reaction of other heterocycles.[146] The general reaction is shown in **Scheme 190** where compound **458** was the desired product.



458

Scheme 190

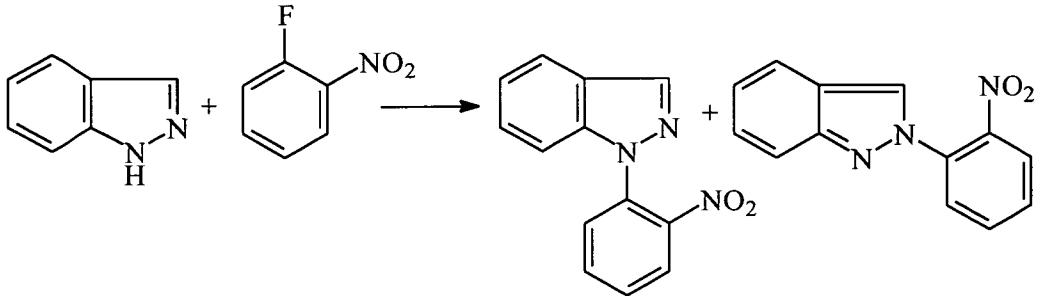
A summary of heterocycles used in this reaction, and the yields of 1-(2-nitrophenyl) substituted heterocycles obtained are shown in **Table 35**.

Heterocycle	Heating period/h	Yield; compound no
Indole	8	84%; **458a**
Carbazole	24	90%; **458b**
3-methylindole	24	65%; **458c**
Indazole	8	57%; **458d**
Benzimidazole	8	81%; **458e**
2-methylbenzimidazole	24	40%; **458f**
2-methylindole	24	34%; **458g**
2-phenylbenzimidazole	24	81%; **458h**

Table 35:- The heterocycles used in the *N*-arylation reaction with *o*-fluoronitrobenzene and the yields of compound **458** obtained.

The arylation of indole, benzimidazole and indazole all occurred with a heating period of 8 h. This was surprising as indole is a poorer nucleophile than both indazole and benzimidazole. The longer reaction time of carbazole would be expected as it is also a poor nucleophile. The extended reaction time is also required for the substituted heterocycles. This is attributed to steric factors.

However, in the case of indazole, there are two unequivalent sites where *N*-arylation can take place, as shown in **Scheme 191**.



458d **459**

Scheme 191

The arylation takes place at both these sites to produce compound **458d** and **459**, and the resultant mixture needs to be recrystallised three times from toluene to give pure compound **458d**. This isomer was identified by comparison with literature spectra[147] and its structure was confirmed by X-ray crystallography. This crystal structure is discussed in **Section E6.4**.

In the case of 2-methylindole, dry flash chromatography was required to purify the 1-(2-nitrophenyl)-2-methylindole from recovered starting materials. The yield for this reaction is 34% and may be improved by a further extension of the heating period. The purification of all the other nitro compounds was carried out by recrystallation from the appropriate solvent.

6.4 Crystal Structure Data.

Crystal structures were obtained for compounds **458a**, **458b**, **458d** and **458f**, so that they could be compared with each other and also with the structures of the methyl esters **401**, **408** and **411**.

The crystal structure of compound **458a** is shown in **Figures 45** and **46** with the associated data contained in **Tables 36** and **37**.

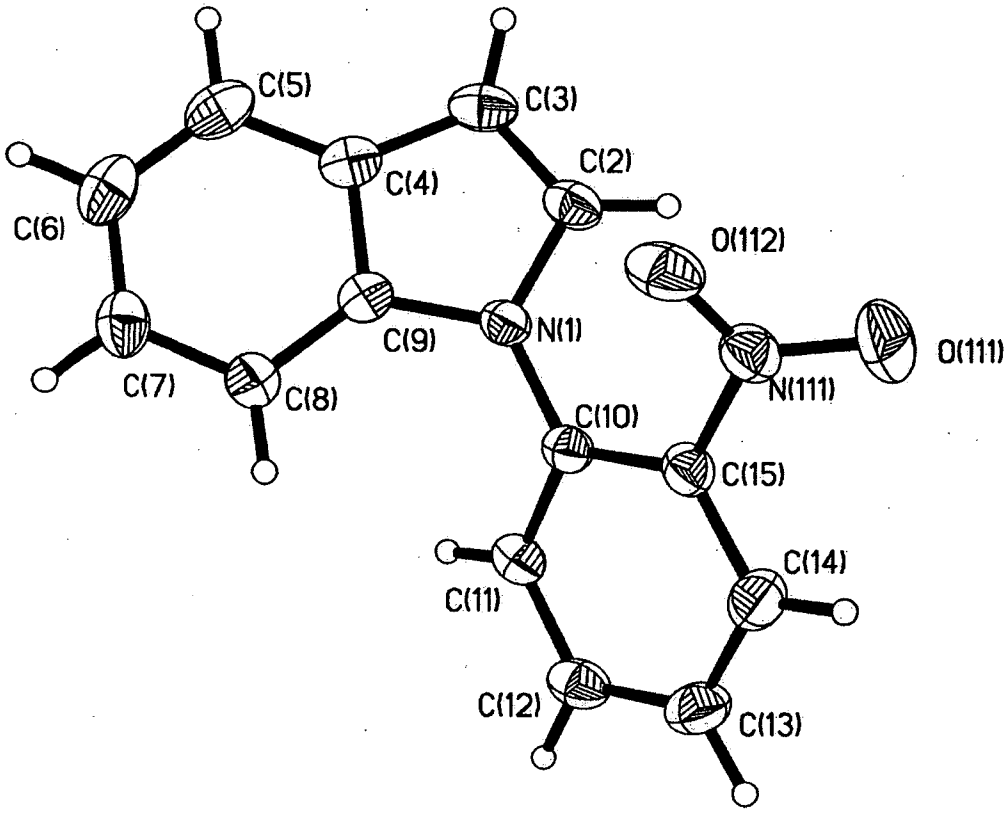


Figure 45

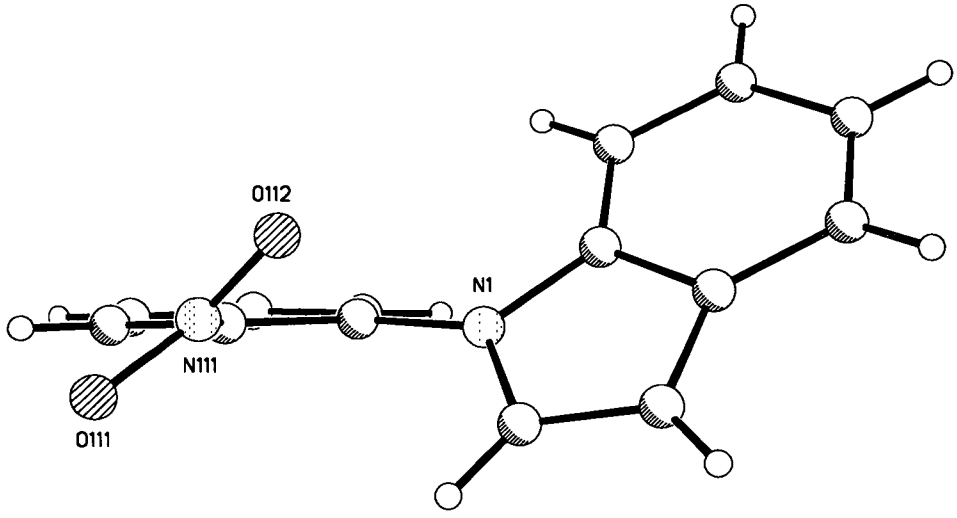


Figure 46

Table 36 Bond Lengths (Å)

N(1) - C(9)	1.3928 (18)
N(1) - C(2)	1.3934 (19)
N(1) - C(10)	1.4097 (18)
C(2) - C(3)	1.341 (2)
C(3) - C(4)	1.430 (2)
C(4) - C(5)	1.399 (2)
C(4) - C(9)	1.407 (2)
C(5) - C(6)	1.370 (3)
C(6) - C(7)	1.396 (2)
C(7) - C(8)	1.379 (2)
C(8) - C(9)	1.391 (2)
C(10) - C(11)	1.388 (2)
C(10) - C(15)	1.393 (2)
C(11) - C(12)	1.377 (2)
C(12) - C(13)	1.376 (2)
C(13) - C(14)	1.376 (2)
C(14) - C(15)	1.382 (2)
C(15) - N(111)	1.4660 (19)
N(111) -O(112)	1.2193 (16)
N(111) -O(111)	1.2196 (17)

Table 37 Bond Angles (degrees)

C(9) - N(1) - C(2)	107.77 (12)
C(9) - N(1) - C(10)	126.21 (12)
C(2) - N(1) - C(10)	125.99 (12)
C(3) - C(2) - N(1)	110.12 (14)
C(2) -C(3) -C(4)	107.71 (14)
C(5) -C(4) -C(9)	118.67 (15)
C(5) -C(4) -C(3)	134.31 (15)
C(9) -C(4) -C(3)	107.01 (13)
C(6) -C(5) -C(4)	119.22 (16)
C(5) -C(6) -C(7)	121.15 (16)
C(8) -C(7) -C(6)	121.36 (16)
C(7) -C(8) -C(9)	117.28 (15)
C(8) - C(9) - N(1)	130.25 (13)
C(8) -C(9) -C(4)	122.31 (14)
N(1) - C(9) - C(4)	107.39 (13)
C(11) - C(10) - C(15)	117.20 (13)
C(11) - C(10) - N(1)	119.79 (13)
C(15) - C(10) - N(1)	112.94 (13)
C(12) - C(11) - C(10)	120.90 (15)
C(13) - C(12) - C(11)	120.87 (15)
C(14) - C(13) - C(12)	119.53 (15)
C(13) - C(14) - C(15)	119.40 (15)
C(14) - C(15) - C(10)	122.03 (14)
C(14) - C(15) - N(111)	116.70 (13)
C(10) - C()15 - N(111)	121.22 (13)
O(112) - N(111) - O(111)	123.79 (14)
O(112) - N(111) - C(15)	118.35 (12)
C(111) - N(111) - C(15)	117.82 (13)

The crystal structure of compound **458b** is shown in **Figures 47** and **48** with the associated data contained in **Tables 38** and **39**.

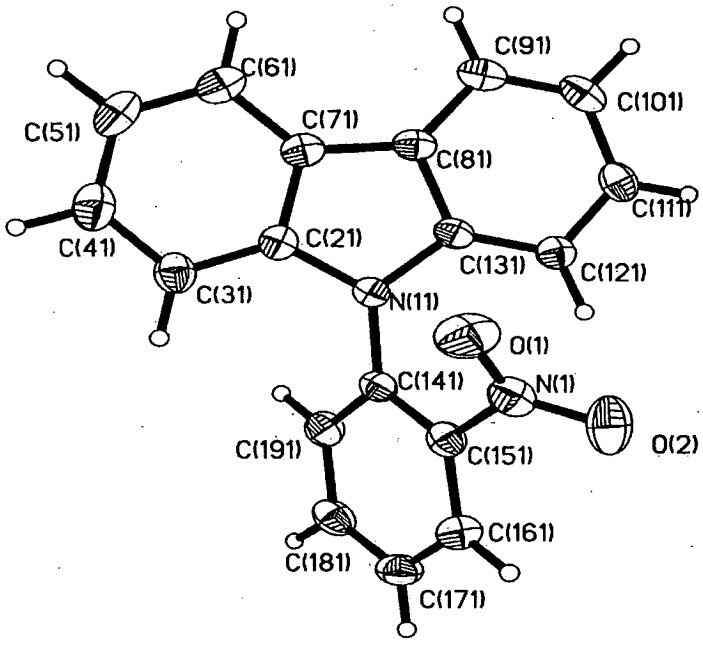


Figure 47

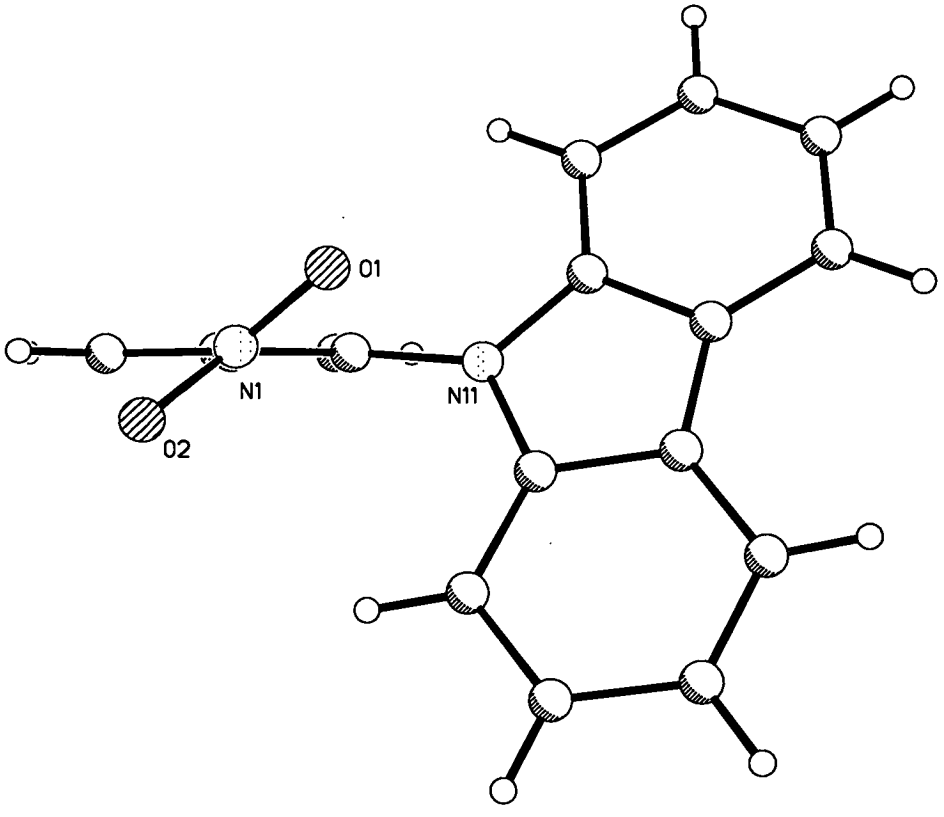


Figure 48

Table 38 Bond Lengths (Å)

N(1) – O(1)	1.2214 (16)
N(1) – O(2)	1.2240 (16)
N(1) – C(151)	1.473 (2)
N(11) – C(131)	1.3947 (17)
N(11) – C(21)	1.3978 (17)
N(11) – C(141)	1.4187 (18)
C(21) – C(31)	1.393 (2)
C(21) – C(71)	1.4047 (19)
C(31) – C(41)	1.384 (2)
C(41) – C(51)	1.396 (2)
C(51) – C(61)	1.373 (2)
C(61) – C(71)	1.4014 (19)
C(71) – C(81)	1.4460 (19)
C(81) – C(91)	1.398 (2)
C(81) – C(131)	1.4106 (19)
C(91) – C(101)	1.378 (2)
C(101) – C(111)	1.401 (2)
C(111) – C(121)	1.390 (2)
C(121) – C(131)	1.393 (2)
C(141) – C(191)	1.3884 (19)
C(141) – C(151)	1.390 (2)
C(151) – C(161)	1.382 (2)
C(161) – C(171)	1.379 (2)
C(171) – C(181)	1.385 (2)
C(181) – C(191)	1.384 (2)

Table 39 Bond Angles (degrees)

O(1) – N(1) – O(2)	124.18 (13)
O(1) – N(1) – C(151)	118.39 (12)
O(2) – N(1) – C(151)	117.40 (12)
C(131) – N(11) – C(21)	108.85 (11)
C(131) – N(11) – C(141)	125.08 (11)
C(21) – N(11) – C(141)	125.84 (10)
C(31) – C(21) – N(11)	129.06 (13)
C(31) – C(21) – C(71)	122.42 (13)
N(11) – C(21) – C(71)	108.52 (11)
C(41) – C(31) – C(21)	116.86 (15)
C(31) – C(41) – C(51)	121.65 (15)
C(61) – C(51) – C(41)	121.15 (15)
C(51) – C(61) – C(71)	118.86 (15)
C(61) – C(71) – C(21)	119.06 (13)
C(61) – C(71) – C(81)	133.72 (14)
C(21) – C(71) – C(81)	107.21 (11)
C(91) – C(81) – C(131)	118.88 (12)
C(91) – C(81) – C(71)	134.19 (12)
C(131) – (81) – C(71)	106.89 (12)
C(101) – C(91) – C(81)	119.38 (13)
C(91) – C(101) – C(111)	120.85 (13)
C(121) – C(111) – C(101)	121.41 (14)
C(111) – C(121) – C(131)	117.13 (13)
C(121) – C(131) – N(11)	129.06 (12)
C(121) – C(131) – C(81)	122.36 (13)
N(11) – C(131) – C(81)	108.53 (12)
C(191) – C(141) – C(151)	117.87 (11)
C(191) – C(141) – N(11)	119.68 (12)
C(151) – C(141) – N(11)	122.32 (12)
C(161) – C(151) – C(141)	122.10 (13)
C(161) – C(151) – N(1)	117.12 (12)
C(141) – C(151) – N(1)	120.78 (12)
C(171) – C(161) – C(151)	119.02 (14)
C(161) – C(171) – C(181)	119.97 (14)
C(191) – C(181) – C(171)	120.45 (14)
C(181) – C(191) – C(141)	120.52 (13)

The crystal structure of compound **458d** is shown in **Figures 49** and **50** with the associated data contained in **Tables 40** and **41**.

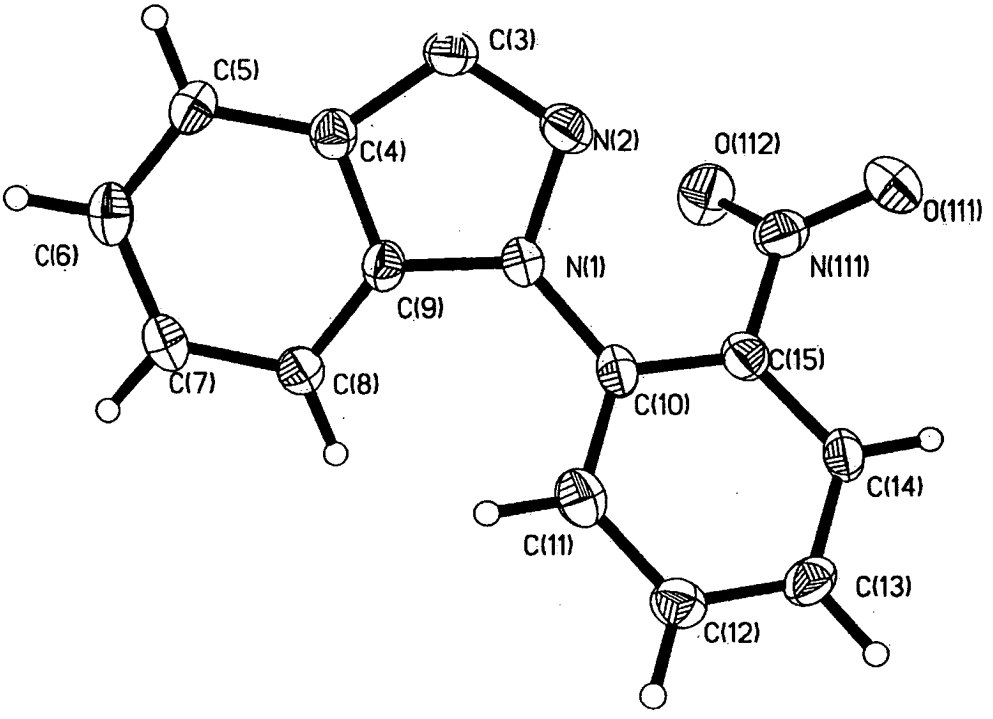


Figure 49

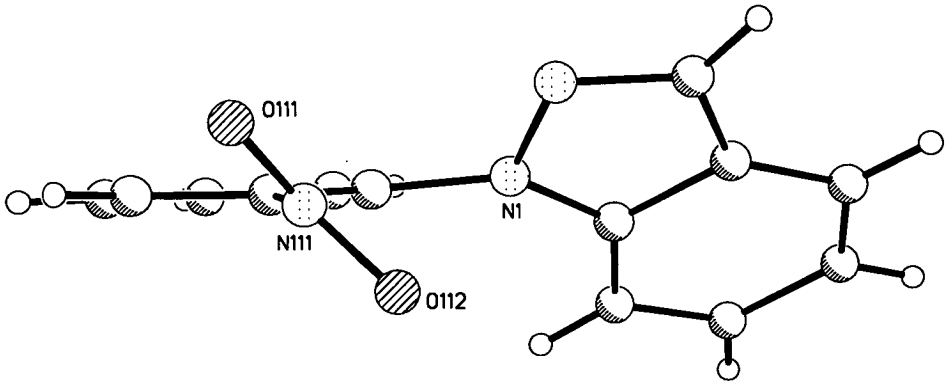


Figure 50

Table 40 Bond Lengths (Å)

N(111) - O(112)	1.196(5)
N(111) - O(111)	1.231 (5)
N(111) - C(15)	1.480(4)
C(14) - C(15)	1.375(5)
C(14) - C(13)	1.390(5)
N(1) - C(9)	1.363(5)
N(1) -N(2)	1.389(4)
N(1) - C(10)	1.409(5)
C(12) - C(13)	1.368(6)
C(12) - C(11)	1.382 (6)
C(10) - C(15)	1.366 (6)
C(10) - C(11)	1.391 (5)
C(4) - C(5)	1.38 (6)
C(4) - C(9)	1.389 (5)
C(4) - C(3)	1.407(6)
C(3) - N(2)	1.317 (5)
C(7) - C(8)	1.375 (6)
C(7) - C(6)	1.395 (5)
C(9) - C(8)	1.392 (5)
C(5) - C(6)	1.372 (6)

Table 41 Bond Angles (degrees)

O(112) - N(111) - O(111)	124.6 (3)
O(112) - N(111) - C(15)	118.8 (4)
O(111) - N(111) - C(15)	116.6 (4)
C(15) - C(14) - C(13)	117.7 (4)
C(9) - N(1) - N(2)	110.8 (3)
C(9) - N(1) - C(10)	129.3 (3)
N(2) - N(1) - C(10)	118.9 (3)
C(13) - C(12) - C(11)	121.5 (3)
C(15) - C(10) - C(11)	118.4 (4)
C(15) - C(10) - N(1)	122.0 (3)
C(11) - C(10) - N(1)	119.5 (4)
C(5) - C(4) - C(9)	119.9 (3)
C(5) - C(4) - C(3)	134.5 (3)
C(9) - C(4) - C(3)	105.6 (4)
C(12) - C(11) - C(10)	119.1 (4)
N(2) - C(3) - C(4)	111.5 (3)
C(3) - N(2) - N(1)	105.5 (3)
C(10) - C(15) - C(14)	123.3 (3)
C(10) - C(15) - N(111)	120.9 (3)
C(14) - C(15) - N(111)	115.7 (4)
C(8) - C(7) - C(6)	121.7 (4)
N(1) - C(9) - C(4)	106.5 (3)
N(1) - C(9) - C(8)	131.2 (3)
C(4) - C(9) - C(8)	122.3 (4)
C(7) - C(8) - C(9)	116.6 (3)
C(6) - C(5) - C(4)	118.3 (4)
C(5) - C(6) - C(7)	121.1 (5)
C(12) - C(13) - C(14)	120.0 (4)

The crystal structure of compound **458f** is shown in **Figures 51** and **52** with the associated data contained in **Tables 42** and **43**.

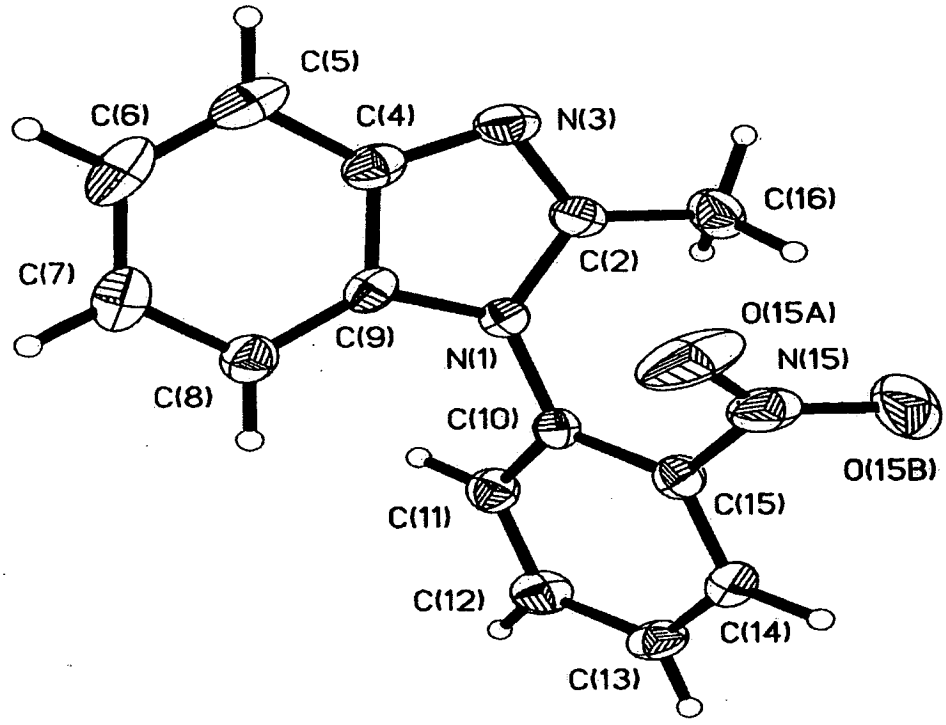


Figure 51

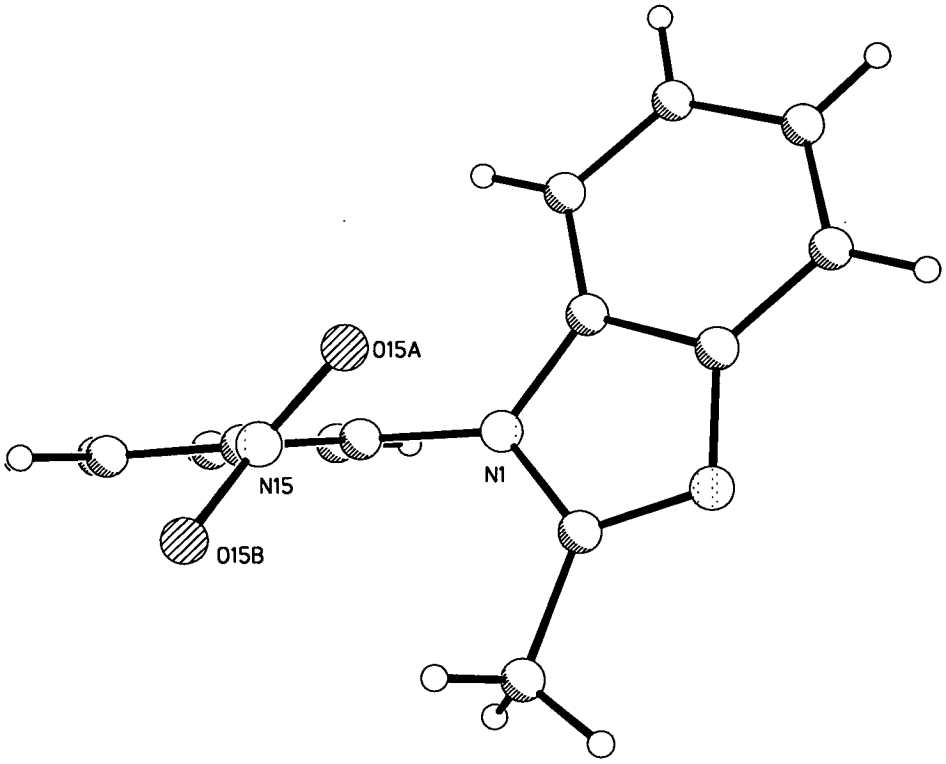


Figure 52

Table 42 Bond Lengths (Å)

N(1) - C(2)	1.379 (2)
N(1) - C(9)	1.388 (2)
N(1) - C(10)	1.422 (2)
C(2) - N(3)	1.304 (2)
C(2) - C(16)	1.486 (3)
N(3) - C(4)	1.390 (3)
C(4) - C(5)	1.395 (3)
C(4) - C(9)	1.398 (3)
C(5) - C(6)	1.376 (3)
C(6) - C(7)	1.395 (3)
C(7) - C(8)	1.385 (3)
C(8) - C(9)	1.385 (3)
C(10) - C(11)	1.382 (3)
C(10) - C(15)	1.391 (2)
C(11) - C(12)	1.380 (3)
C(12) - C(13)	1.384 (3)
C(13) - C(14)	1.377 (3)
C(14) - C(15)	1.374 (3)
C(15) - N(15)	1.464 (2)
N(15) - O(15A)	1.219 (2)
N(15) - O(15B)	1.221 (2)

Table 43 Bond Angles (degrees)

C(2) - N(1) - C(9)	106.54 (15)
C(2) - N(1) - C(10)	127.53 (15)
C(9) - N(1) - C(10)	125.54 (14)
N(3) - C(2) - N(1)	113.03 (17)
N(3) - C(2) - C(16)	124.56 (17)
N(1) - C(2) - C(16)	122.39 (17)
C(2) - N(3) - C(4)	105.20 (15)
N(3) - C(4) - C(5)	130.05 (18)
N(3) - C(4) - C(9)	110.27 (16)
C(5) - C(4) - C(9)	119.68 (19)
C(6) - C(5) - C(4)	117.6 (2)
C(5) - C(6) - C(7)	121.88 (19)
C(8) - C(7) - C(6)	121.5 (2)
C(9) - C(8) - C(7)	116.15 (19)
C(8) - C(9) - N(1)	131.92 (17)
C(8) - C(9) - C(4)	123.11 (17)
N(1) - C(9) - C(4)	104.97 (16)
C(11) - C(10) - C(15)	117.85 (16)
C(11) - C(10) - N(1)	120.49 (16)
C(15) - C(10) - N(1)	121.65 (16)
C(12) - C(11) - C(10)	120.36 (18)
C(11) - C(12) - C(13)	120.67 (18)
C(14) - C(13) - C(12)	119.80 (18)
C(15) - C(14) - C(13)	118.94 (18)
C(14) - C(15) - C(10)	122.35 (17)
C(14) - C(15) - N(15)	117.73 (16)
C(10) - C(15) - N(15)	119.91 (16)
O(15A) - N(15) - O(15B)	124.80 (19)
O(15A) - N(15) - C(15)	118.09 (18)
O(15B) - N(15) - C(15)	117.11 (19)

Figure 53 shows compounds **458a**, **458b**, **458d** and **458f** with some of their bond lengths shown.

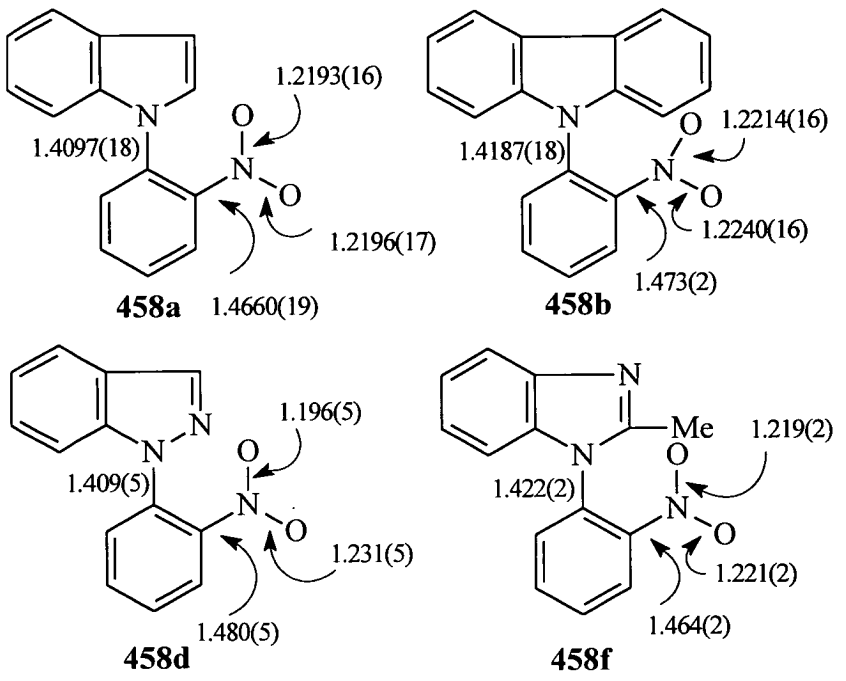


Figure 53

There are no significant differences in bond lengths around the nitro compounds in these four compounds. However, it should be noted that in all four compounds the N-C bond linking the benzene ring and nitro group is the longest bond, and is significantly longer than the *N*-aryl bond.

The angles between the plane of the heterocycle (indazole, 2-methylbenzimidazole, indole and carbazole), the plane of the benzene ring substituted on the nitrogen atom and the nitro group are shown in **Table 44**.

Compound	Angle between the heterocycle plane and the *N*-aryl plane.	Angle between the *N*-aryl plane and the nitro group plane.
458a	47.17(4)	41.11(6)
458b	61.11(5)	40.48(9)
458d	40.29(11)	47.35(27)
458f	68.64(5)	47.31(17)

Table 44:- Angles between the planes of compounds **458a**, **458b**, **458d** and **458f**.

It can be seen in **Figures 46**, **48**, **50** and **52** that the nitro group has bent out of the plane of the *N*-aryl group by a significant angle. It should be noted that these angles

are significantly different from those for the methyl ester compounds discussed in **Section D**. These values are shown in **Table 34**. The angles between the heterocycle plane and the *N*-aryl plane for the esters are ~63° which is much higher than for compounds **458a** and **458d** but in the same range as compounds **458b** and **458f**. However, the angle between the *N*-aryl plane and the nitro group plane in the ester compounds is ~34° which is significantly smaller than the corresponding angles in the nitro compounds.

The deformation of the *ortho* nitro group out of the *N*-aryl plane and the longest bond linking the nitro group and *N*-aryl group in compounds **458a**, **458b**, **458d** and **458f**, suggests that this bond may be weaker and should break under pyrolysis conditions. This is because the deformation of the *ortho* nitro group disrupts its conjugation with the aryl group.

This suggestion is supported by the crystal structure of 1-(2,4-dinitrophenyl)pyrazole.[148] A schematic is shown in **Figure 54**.

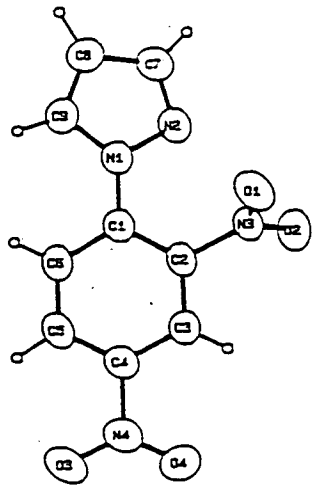


Figure 54

The torsion angle between O2-N3-C2-C3 is 69.13(14)° and between O1-N3-C2-C1 is 66.9(2)°. This again shows that the *ortho* nitro group is significantly bent out of the plane of the *N*-aryl group. The torsion angle between O4-N4-C4-C3 is 8.4(2)° which shows that the *para* group is not significantly bent out of the plane of the *N*-aryl group.

This may also account for the contradictory nature of the literature on the pyrolysis reactions of nitro compounds. In the reactions by Rees and De Mayo, the nitro compounds were *ortho* substituted and this resulted in phenyl radicals

suggesting that there was a deformation of the nitro group out of the plane of the aryl ring. As described above, this would cause disruption in the conjugation of the nitro group and aryl ring, making the bond linking them weaker and more likely to break under pyrolysis conditions. In the work by Fields, Meyerson and Wiersum, the nitro compounds were not *ortho* substituted. Therefore, there would be no deformation of the nitro group out of the aryl plane. This would mean that the conjugation of the nitro group and aryl ring would not be disrupted, and the bond linking them would be less likely to break when pyrolysed, which would explain the rearrangements that were observed.

6.5 Pyrolysis of 1-(2-nitrophenyl) substituted heterocycles.

Small-scale pyrolysis reactions of these derivatives were carried out using a U-tube trap as previously described. However, when these reactions were repeated on a large (0.5 g and above) scale, the product decomposed in the U-tube trap. It is noted that attempts to cool this sidearm of the U-tube using dry ice, caused the product to collect inside the furnace tube, where it decomposed thermally. An alternative trapping system was designed where the appropriate derivative was sublimed, under vacuum, through the furnace tube, and the product(s) were collected in a cold finger trap which was at the exit point of the furnace and was cooled with dry-ice and acetone. (The joint between this trap and the furnace tube was pushed into the furnace to ensure that the majority of the product solidified on the cold finger and not on the sidearm, so that decomposition of the product was minimised). The cold-finger trap had a U-tube connected in series which was cooled with liquid nitrogen to trap the nitrogen oxide co-product. Upon completion of the pyrolysis, nitrogen gas was released through the system, which was then taken apart before the U-tube could warm to room temperature (This prevented the product in the cold-finger trap coming into contact with the reactive nitrogen gases again), and the U-tube was placed in a fume-cupboard to allow it to warm to room temperature. The dry ice/acetone mixture was poured from the cold-finger which was then immediately dismantled. Care was taken to avoid the product coming into contact with any greased joints. The product was quickly washed off using dichloromethane to prevent water from condensing on it. The product was then subjected to normal

purification procedures. All these large scale pyrolysis reactions were carried out using this trapping system.

6.5.1 Fate of the nitro group.

During these pyrolyses, derivatives of the nitro group are collected in a second U-tube in series. There is a distinct blue solid at the liquid nitrogen level of this U-tube, which turns to a brown gas as it warms to room temperature. The blue liquid is thought to be dinitrogen trioxide. This oxide is formally the anhydride of nitrous acid.

$$N_2O_3\,(g) \rightleftharpoons NO\,(g) + NO_2\,(g)$$

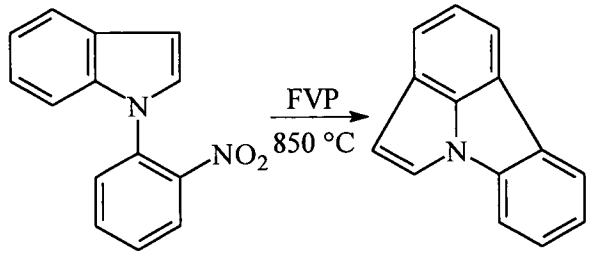
Scheme 192

The brown gas is thought to be NO_2 which also fits with the above equilibrium and can be derived from the dinitrogen trioxide.[149] This is shown in **Scheme 192**.

No attempts were made to trap this gas or characterise it.

6.5.2 Pyrolysis reactions of 1-(2-nitrophenyl) substituted indole, carbazole and 3-methylindole.

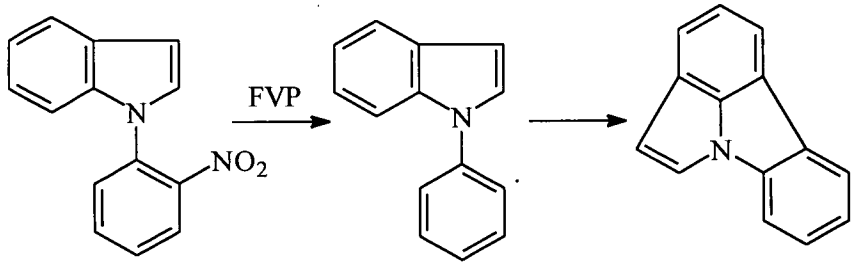
Compound **458a** was pyrolysed at 850 °C and resulted in the expected pyrrolo[3,2,1-*jk*]carbazole **361** in 33% yield after chromatography, as shown in **Scheme 193**.



458a **361**

Scheme 193

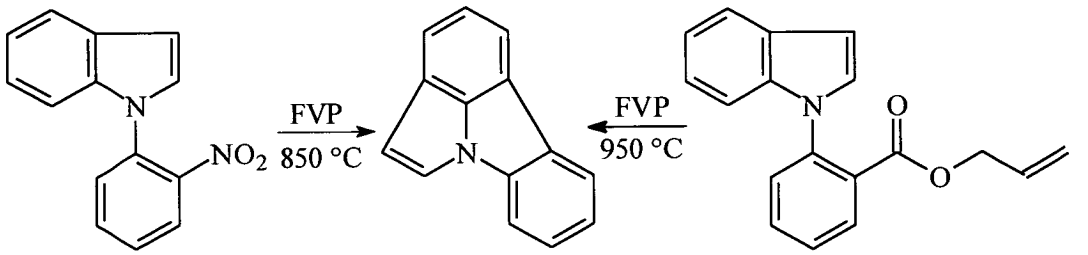
The proposed mechanism for this reaction is shown in **Scheme 194**.



458a **368** **361**

Scheme 194

Compound **458a** pyrolyses to give phenyl radical **368** which then cyclises with loss of a hydrogen atom to give compound **369**.



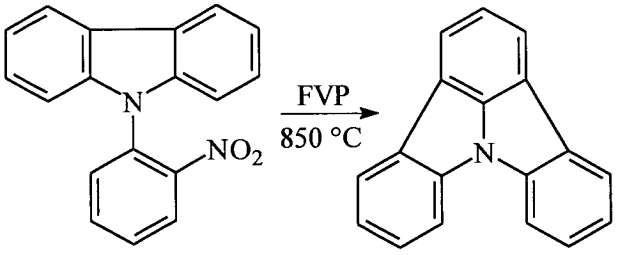
458a **361** **393**

Scheme 195

The pyrolysis of nitro compound **458a** produces compound **361** in 33% yield, however, compound **361** is produced in 42% yield from allyl ester **393**, as shown in **Scheme 195**. This suggests that the pyrolysis of the allyl ester precursor is more efficient than the corresponding pyrolysis of nitro compound **458a**. However, it should be noted that the synthesis of precursor **458a** is more straightforward than that of compound **393**.

This experiment suggests that these nitro compounds are suitable precursors for the pyrolytic synthesis of the desired multicyclic compounds.

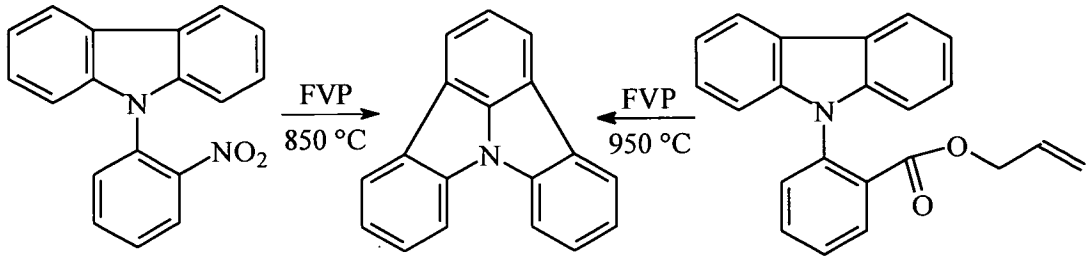
Compound **458b** was pyrolysed and resulted in the formation of compound **398**, as expected, in 48% yield, as shown in **Scheme 196**.



458b **398**

Scheme 196

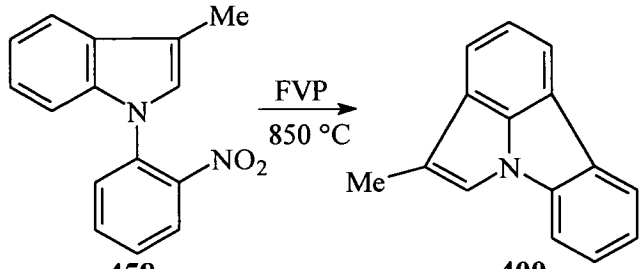
Again, the crude pyrolysate was very clean with the compound **398** being the only product. Compound **458b** pyrolyses to compound **398** in 48% yield whereas compound **398** is produced in 60% from the pyrolysis of compound **406**, as shown in **Scheme 197**. This again illustrates that the pyrolysis of the allyl ester **406** is more efficient than the corresponding pyrolysis of nitro compound **458b**.



458b **398** **406**

Scheme 197

When compound **458c** was pyrolysed, the ^{1}H NMR spectrum of the crude pyrolysate was not as "clean" as those obtained for the pyrolysis of compounds **458a** and **458b**. The major product was 4-methylpyrrolo[3,2,1-*jk*]carbazole **400** which was identified by comparison with an authentic spectrum, as shown in **Scheme 198**.



458c **400**

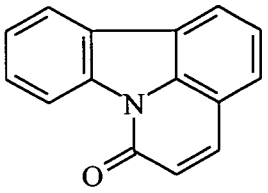
Scheme 198

The yield for compound **400** was obtained from the ^{1}H NMR spectrum after the addition of a known quantity of cyclohexane and was 27%. The other products obtained in this pyrolysis were not identified as they could not be separated by dry flash chromatography. Compound **400** was also synthesised by the pyrolysis of allyl ester **408** in 28% yield. In this example, the allyl ester pyrolysis does not seem to be much more efficient than that of the corresponding nitro compound. However, it should be noted that the yield for the pyrolysis of nitro compound **458c** is not a preparative yield.

The results of these pyrolysis reactions suggest that the pyrolysis reaction of the nitro compounds are not as efficient as that of the corresponding allyl ester compounds. The synthesis of these pyrolysis precursors is much easier, making this the method of choice from a practical point of view.

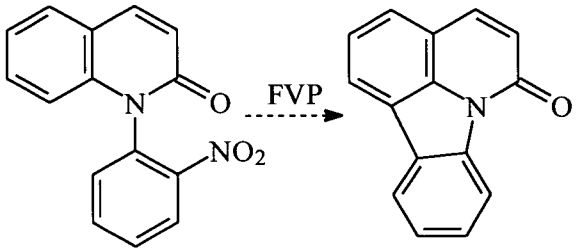
6.5.3 Attempted Natural Product Synthesis.

Compound **460** is a cytotoxic alkaloid and has been isolated from *Fagara viridis*[150] in small quantities. There are also some reported small scale syntheses of this compound.[151, 152]



460

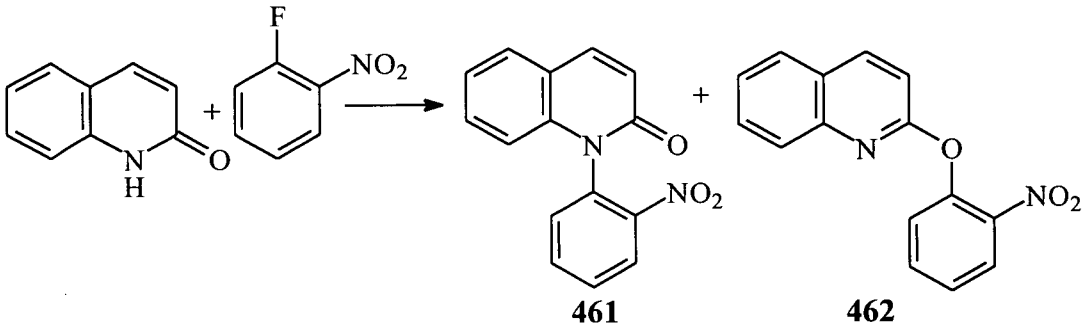
It was anticipated that the cyclisation reactions described in **Section E6.5.2** could potentially be used in the synthesis of compound **460**, as shown in **Scheme 199**, where compound **461** could potentially give compound **460** on pyrolysis.



461 **460**

Scheme 199

1*H*-Quinolin-2-one was subjected to the arylation conditions of heating overnight in DMF with potassium carbonate at 125 °C. However, there are two possible arylation sites in 1*H*-quinolin-2-one. One isomer was obtained and it could either be the *N*-arylated isomer **461** or the *O*-arylated isomer **462**, as shown in **Scheme 200**.

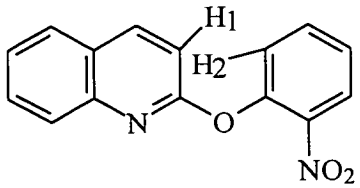


461 **462**

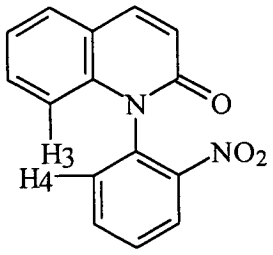
Scheme 200

Several different methods were employed to identify this isomer. An infrared spectrum of this compound was obtained, and showed no distinguishing absorptions. If compound **461** was obtained, a strong characteristic carbonyl stretch in the range

1600 - 1700 cm^{-1} would be expected. [It should be noted that in **Section A**, 1*H*-quinolin-2-one was alkylated with α,4-dichloroanisole. NOe experiments were used to distinguish between the isomers as infrared spectroscopy gave inconclusive results.] Compound **462** is a known compound, and its melting point has been reported as 108 - 109 °C.[153] The melting point of the obtained isomer was 110 - 111 °C, which suggests that it was compound **462**. In order to further confirm the identity of this compound, it was subjected to an NOESY NMR experiment.



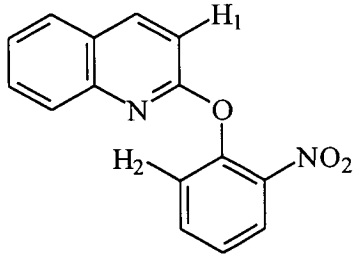
462



461

Figure 55

If the isomer was compound **462**, then the NOESY experiment should show a correlation from proton H_1 to H_2, and if the isomer was compound **461**, then the NOESY experiment should show a correlation from proton H_3 to H_4, as shown in **Figure 55**. However, no inter-ring correlations appeared on the NOESY experiment which suggests that compound **462** actually exists predominantly as shown in **Figure 56**.



462

Figure 56

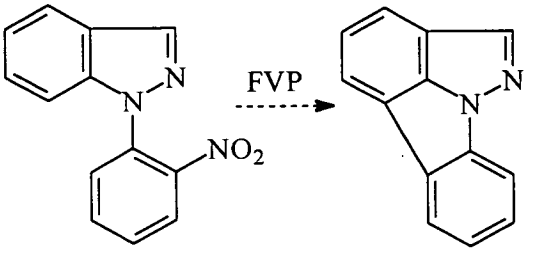
In this case the protons H_1 and H_2 would be too far apart to display an nOe correlation on the NOESY NMR spectrum.

The pyrolysis of this compound also produced a messy crude proton NMR spectrum. By comparison with authentic spectral data, compound **460** and its decarbonylation product, compound **361**, were eliminated as products from the

pyrolysate. The obtained products could not be separated by dry flash chromatography and therefore were not identified. Other methods of *N*-arylation of this compound were not investigated and this still may be a potential route to compound **460**.

6.5.4 Pyrolysis of 1-(2-nitrophenyl) substituted indazole and benzimidazole.

This work was extended to the investigation of the 1-(2-nitrophenyl)substituted benzimidazole and indazole. It was anticipated that compound **458d** would result in compound **463**, as shown in **Scheme 201**, by analogy with the cyclisation reactions of compounds **458a**, **458b** and **458c**.



458d **463**

Scheme 201

However, the pyrolysis of compound **458d** gave a product in 59% yield. Although this product showed the expected *m/z* value of 192, the ^{1}H and ^{13}C NMR spectra were not consistent with those expected for **463**.

The proton spectrum for compound **464** is shown in **Figure 57**. This shows a broad signal at ~9.05 ppm which could be due to an N-H signal, or it could be a broadened C-H peak such as those observed in **Figure 41**. A proton-carbon correlation experiment was carried out, and the absence of a correlation for this broadened signal suggested that it was a N-H signal. This is shown in **Figure 58**. The ^{13}C NMR spectrum has seven C-H peaks, whereas eight would be expected for compound **463**. It also has a quaternary signal at ~95 ppm which would be unusual for **463**. The compound was then subjected to infrared spectroscopy which showed an N-H stretch at 3312.2 cm^{-1} and also at 2223.4 cm^{-1}, which is the characteristic region for a cyano group stretch. Compound **463** was the expected product, and the only way that a N-H signal and cyano group could appear in the product is if bond "a" was to break. This would result in 1-cyanocarbazole, as shown in **Scheme 202**. The identity of this compound was confirmed by comparison with literature spectra.[154]

Proton spectrum for compound **464**.

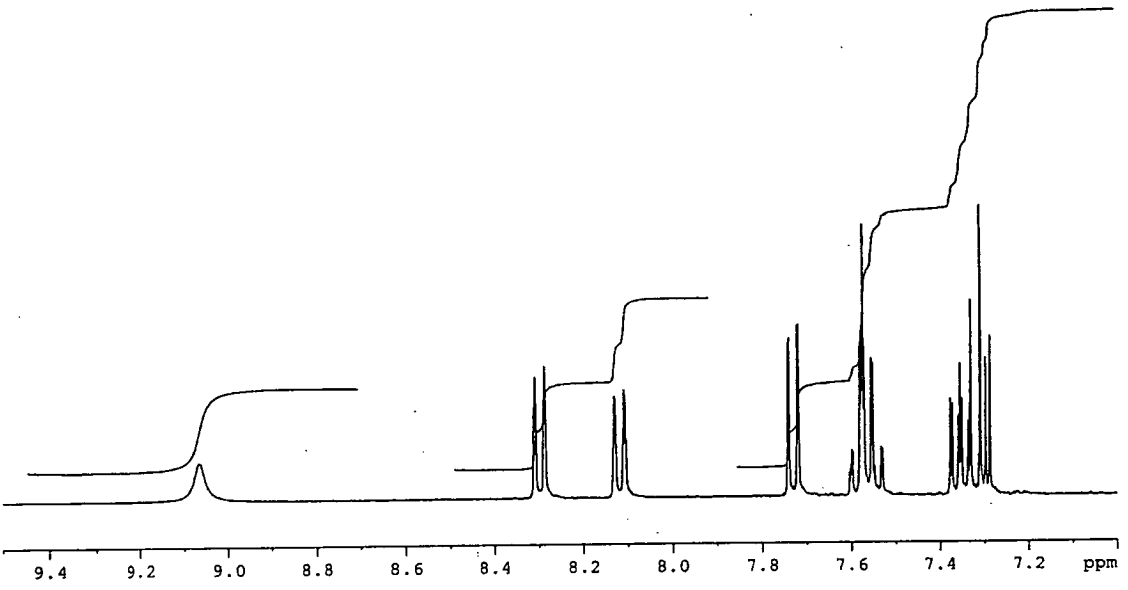


Figure 57

Proton-carbon correlation for compound **464**.

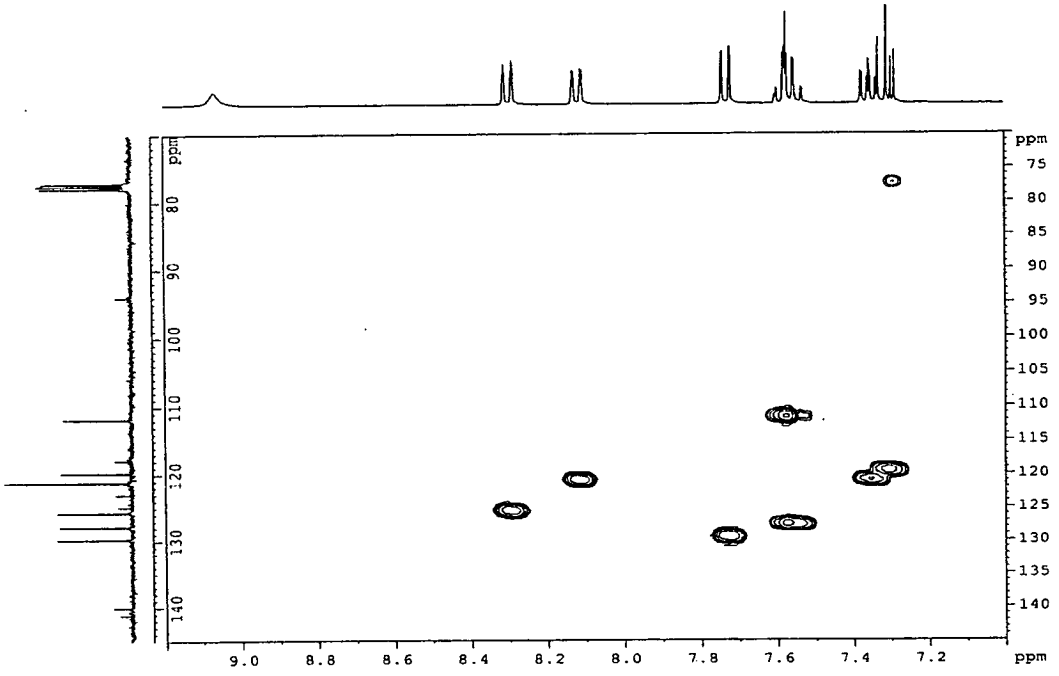
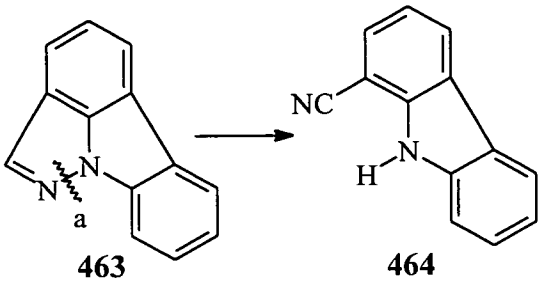


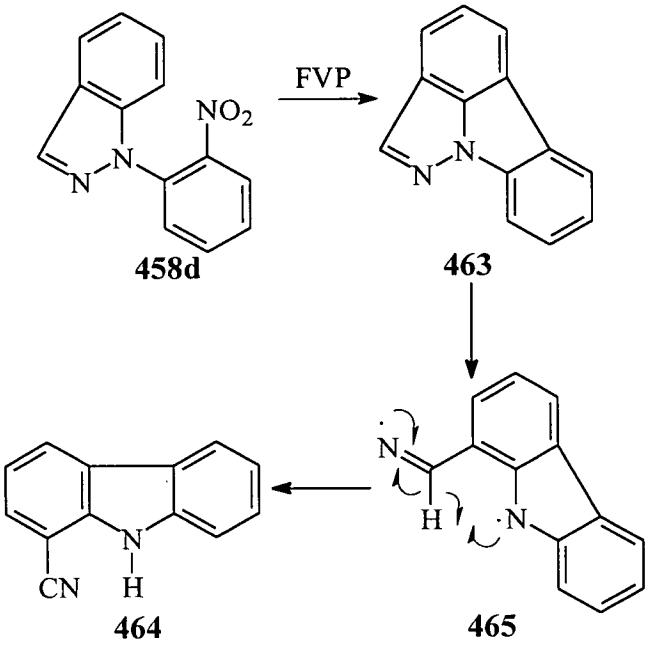
Figure 58



463 **464**

Scheme 202

A proposed mechanism for the formation of 1-cyanocarbazole is shown in **Scheme 203.**

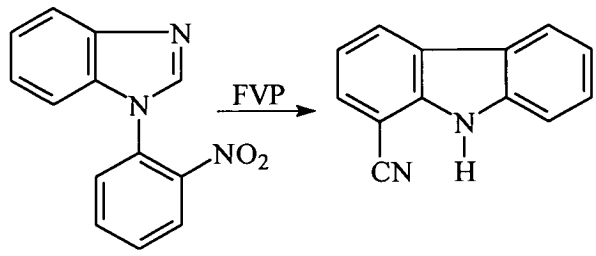


458d **463** **464** **465**

Scheme 203

Compound **458d** pyrolyses to give tetracycle **463**. However, this structure is unstable under the pyrolysis conditions, and the weak N-N bond breaks to give diradical **465** which can rearrange to give 1-cyanocarbazole **464**.

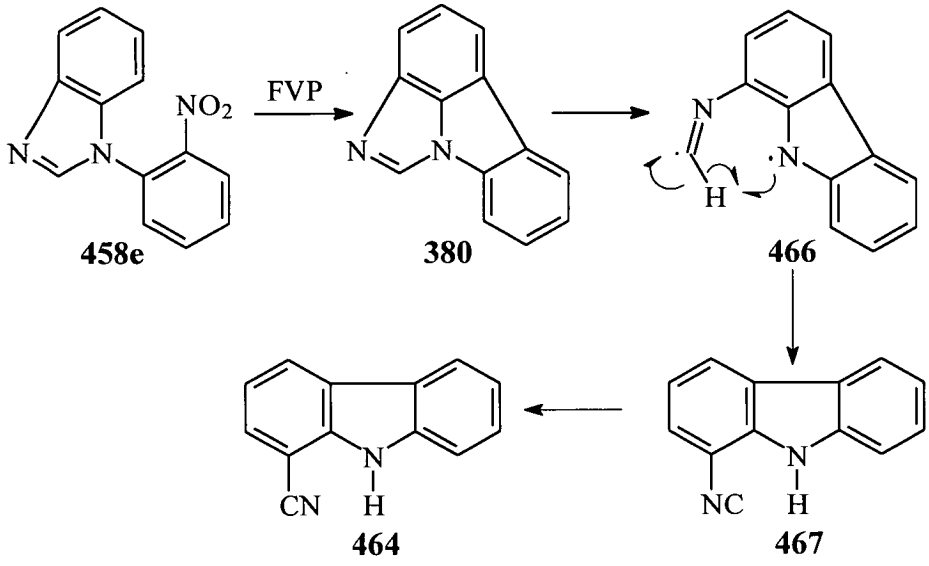
Surprisingly, the pyrolysis of compound **458e** also resulted in 1-cyanocarbazole **464**, as shown in **Scheme 204**.



458e **464**

Scheme 204

The proposed mechanism for this reaction is shown in **Scheme 205**.



458e **380** **466**

464 **467**

Scheme 205

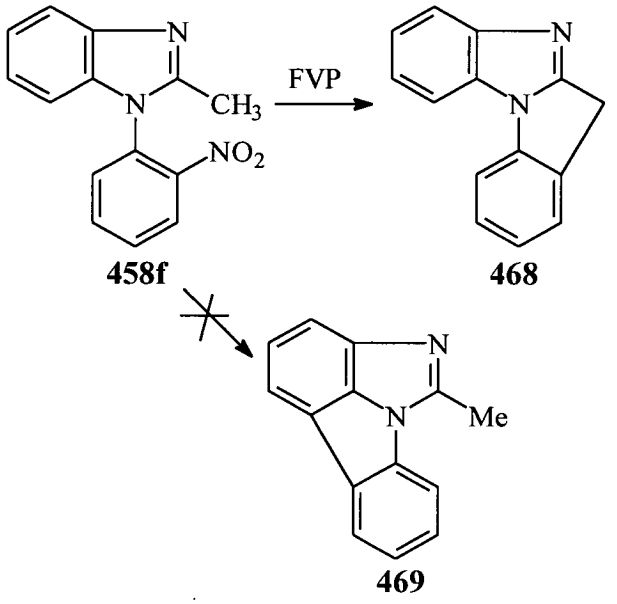
Pyrolysis of compound **458e** gives compound **380** which again ring opens to give the diradical **466**. This can rearrange to the isocyanide **467** (this rearrangement could also occur *via* a three-membered ring in a similar manner to that shown in **Scheme 184**) which can subsequently form the cyano compound **464**. This isocyanide-cyano rearrangement has a literature precedent.[155] The ring-opening of **380** is surprising, as compound **380** does not contain a weak N-N bond as compound **463** did.

In the pyrolysis reactions of compounds **458d** and **458e**, the expected compounds were **463** and **380** respectively. However, neither of these compounds were isolated which must be due to the increased ring strain in compounds **463** and **380**. This causes them to be unstable under the pyrolysis conditions resulting in 1-cyanocarbazole in both cases.

6.5.5 Pyrolysis of 1-(2-nitrophenyl) substituted 2-substituted benzimidazoles and indole.

This work was extended to the investigation of 1-(2-nitrophenyl) substituted 2-substituted benzimidazoles and indole.

Compound **458f** was pyrolysed at 850 °C, but did not produce compound **469** which would be analogous with the cyclisation reactions previously described. Instead compound **468** was produced exclusively in 49% yield, as shown in **Scheme 206**.



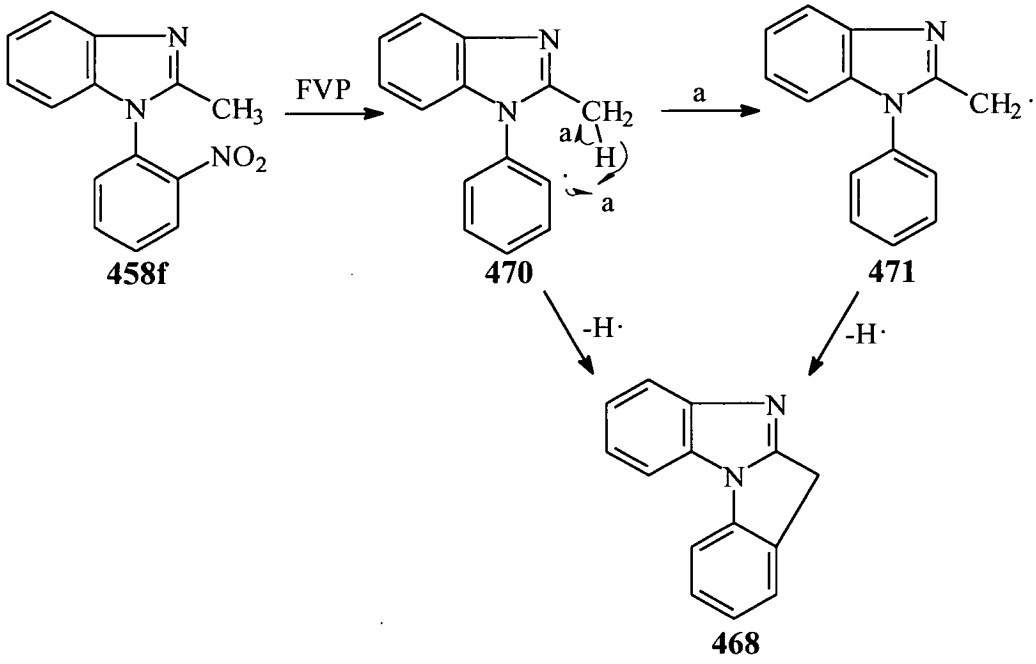
Scheme 206

This compound was identified by its ^{13}C NMR spectrum which showed the presence of a CH_2, peak but no CH_3 peak. This suggested that the cyclisation reaction had to occur onto the methyl group.

The purification of compound **468**, after the large scale pyrolysis, proved to be difficult as recrystallisation, distillation and chromatography all resulted in no identifiable products. Therefore, compound **468** was sublimed on a small scale and characterisation was carried out on the small amount of product. This small scale sublimation was carried out quickly (due to decomposition of the product on larger scale distillation), and a small amount of purified compound **468** was obtained. Characterisation was carried out on the small amount of product.

The alternative course of this reaction suggests that the phenyl radical **470** may either cyclise directly onto the methyl group by a S_H^i [substitution, homolytic,

intramolecular][106, 156] substitution reaction of a hydrogen atom, or it could abstract a hydrogen atom from the methyl group to form radical **471** which could then cyclise to form compound **468** (pathway "a"). This would occur if radical **471** was more stable than radical **470** and is shown in **Scheme 207**.

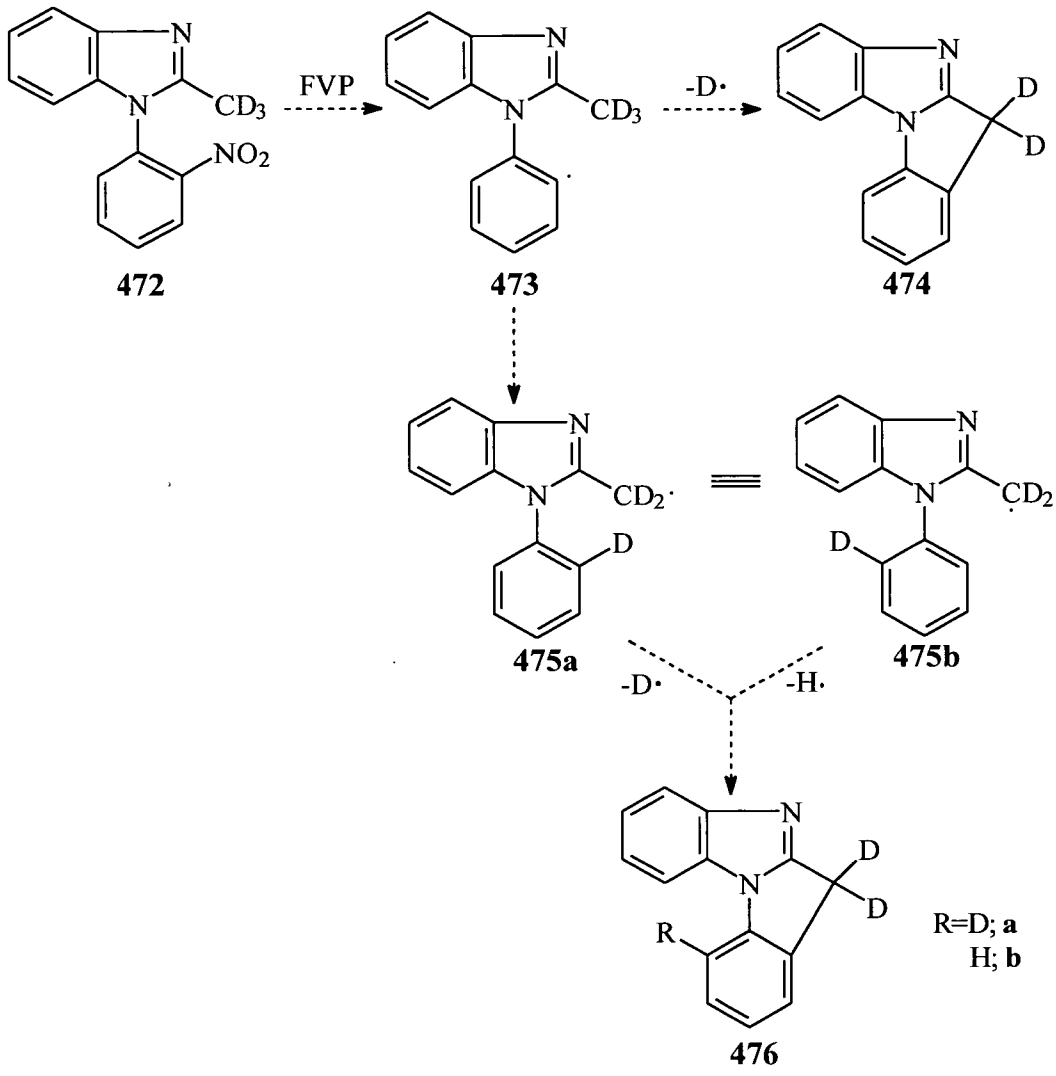


Scheme 207

Deuterium labelling experiments were used to investigate this mechanism. It was anticipated that the pyrolysis of compound **472** would result in either **474**, **476a** or **476b**, as shown in **Scheme 208**.

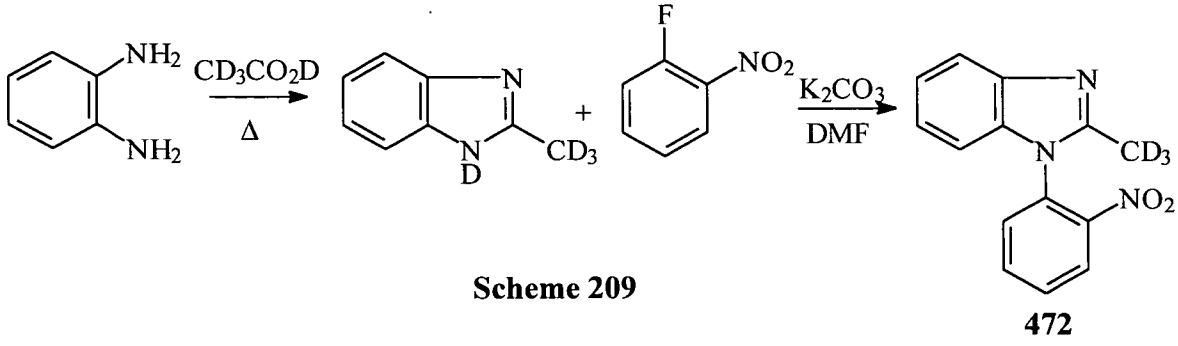
If a direct cyclisation occurred and a deuterium atom was lost, then compound **474** would be observed where the deuterium only occurs at the CD_2 position. However, if the radical **473** rearranged to intermediate **475a** which is equivalent to radical **475b** then either a hydrogen atom or a deuterium atom would be lost and would result in compound **476**. Hydrogen is more likely to be lost as $k_H/k_D \sim 2$ in FVP reactions and hence compound **476** would be the expected product with deuterium in the ratio 3:1 (methylene: aromatic).

[If intermediate **473** goes to intermediate **475a/475b**, then the KDE suggest that hydrogen is more likely to be lost giving 0.7D in the R position in **476** and 2D in the methylene position. This results in a 1:3 ratio.]



Scheme 208

Compound **472** was synthesised *via* a similar arylation method to the unlabelled compound **458f** and was obtained in 33% yield, as shown in **Scheme 209**. The labelled 2-methylbenzimidazole **472** was synthesised in 42% yield by an extension of a literature route to 2-methylbenzimidazole.[157]

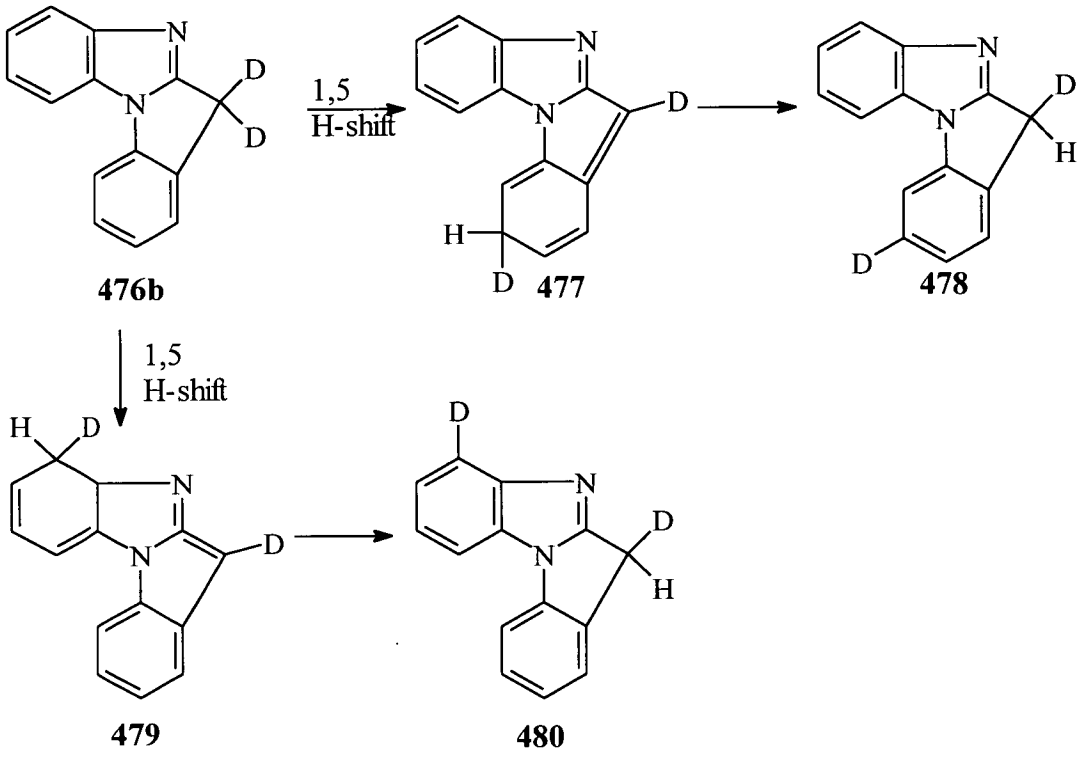


Scheme 209

Compound **472** was subjected to FVP conditions at 850 °C and a deuterium spectrum of the pyrolysate was obtained and is shown in **Figure 59**.

The deuterium spectrum shows that there is a lot of deuterium incorporated in the aromatic region and although there is some incorporated at the methylene group, there is much less than anticipated. The ratio of deuterium peaks is 2:2:2:1 with the smaller peak occurring at the methylene position.

This can be partially rationalised by 1,5-hydrogen shifts. If compound **476b** undergoes a 1,5 hydrogen shift, it will produce compound **478** *via* intermediate **477**. Compound **476b** can also undergo an alternative 1,5-shift to give **480** *via* **479**, as shown in **Scheme 210**.



Scheme 210

Figure 60 shows the expected deuterium incorporation at each site, due to the 1,5-hydrogen shifts. This is based on the K.D.E~2 in an FVP reaction.

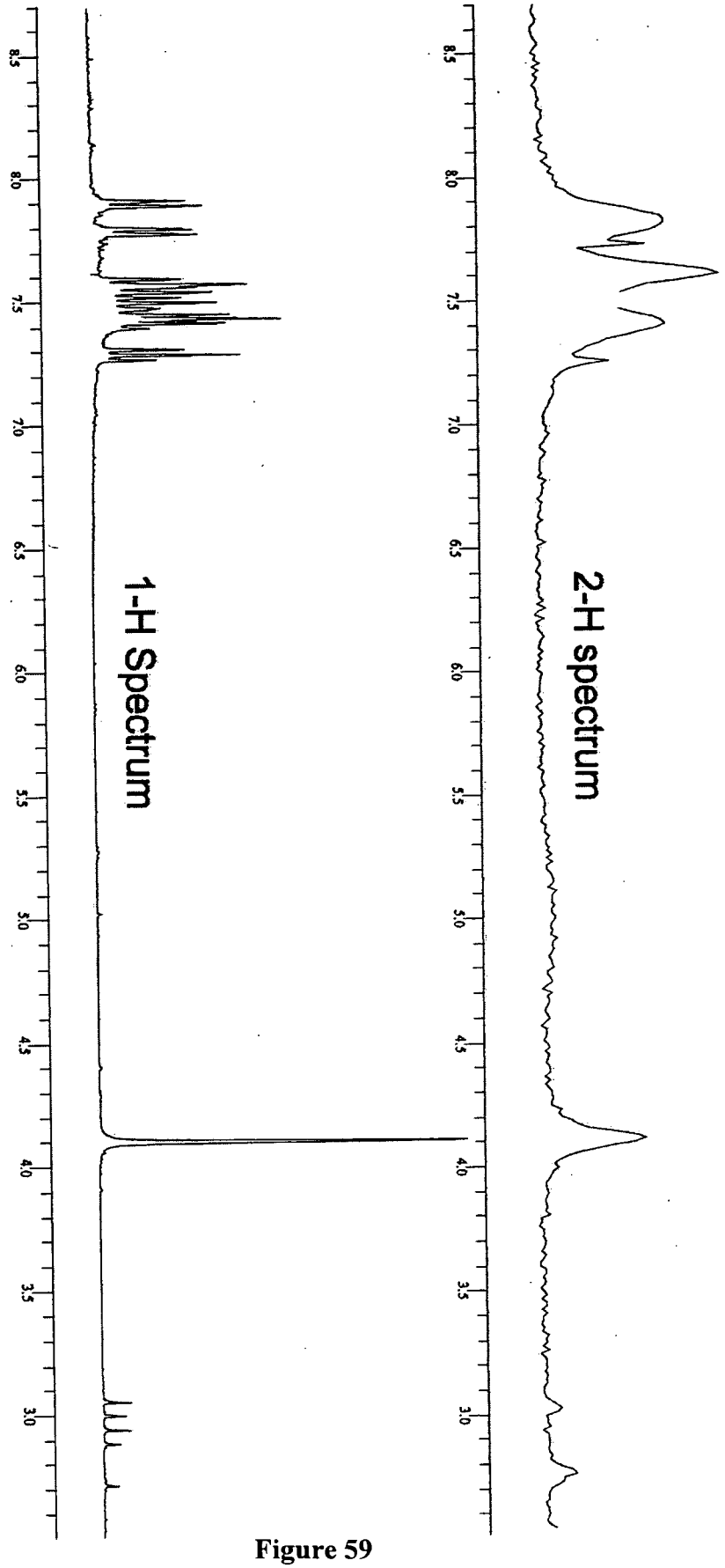


Figure 59

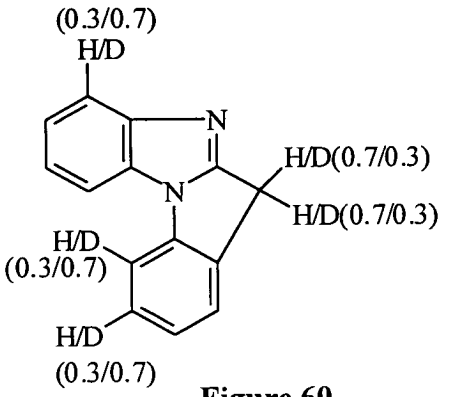
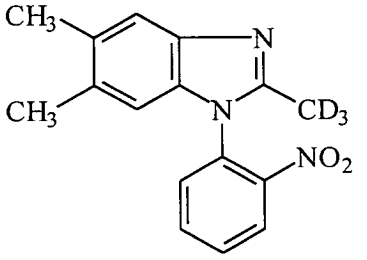


Figure 60

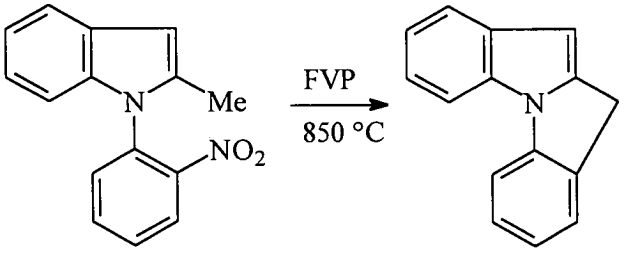
Therefore, you would expect the peak at 4.0 ppm to be of the same intensity as the three aromatic peaks. It should be noted that control experiments were not carried out to see if there were any solvent effects. The chloroform used as an NMR solvent was not purified and may have washed deuterium out of a site. This mechanism is currently under further investigation.

This suggests that there could be deuterium in three aromatic sites, but the aromatic region of non-deuteriated compound **468** is complex and cannot be fully assigned. Therefore, if compound **481** was used as a precursor, the aromatic region would be simpler and the full mechanism may be elucidated from this.



481

The 2-methylindole derivative **458g** was pyrolysed, and also underwent this alternative cyclisation reaction to give compound **482** in 51% yield, as shown in **Scheme 211**.



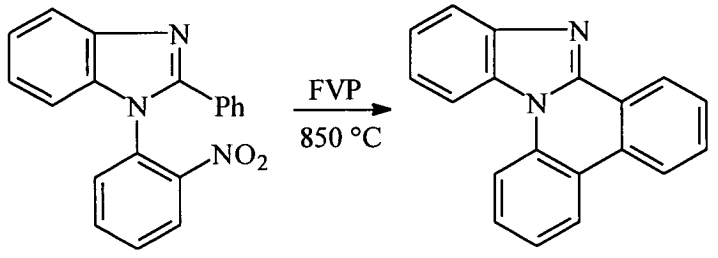
458g **482**

Scheme 211

Again, this product was difficult to purify, and a similar method as for compound **468** was used for characterisation.

Although these derivatives did not undergo the same cyclisation reaction, several other derivatives have been made in good yield and this seems to be a useful method to the synthesis of a 5,5-bicyclic core for a molecule, which has the potential to have other fused rings around it.

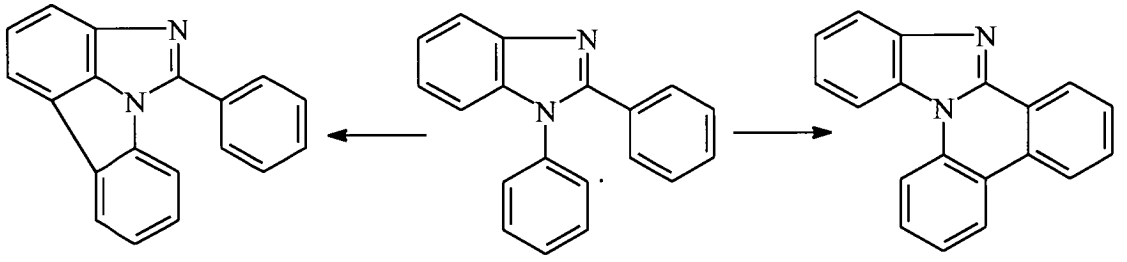
Compound **458h** was pyrolysed and also undergoes an alternative reaction to produce compound **450** as shown in **Scheme 212**, in 35% yield.



458h **450**

Scheme 212

In this case, radical **483** could cyclise with the aryl group in the 2-position to form compound **450**, or it could cyclise with the other aryl group to produce compound **484**, as shown in **Scheme 213**.



484 **483** **450**

Scheme 213

However, compound **450** is produced exclusively as it is less strained than compound **484**.

Compound **450** was initially identified by comparison with literature data.[143] However, the literature proton spectrum was not assigned, therefore compound **450** was subjected to proton, carbon, NOESY, COSY, TOCSY and proton-carbon correlation NMR experiments so that a full assignment could be carried out.

The proton spectrum for compound **450** is shown in **Figure 61** and arbitrarily labelled from left to right, A, B, C, D, E, F, G, H, I, J, K and L.

^{1}H NMR spectrum of compound **450**.

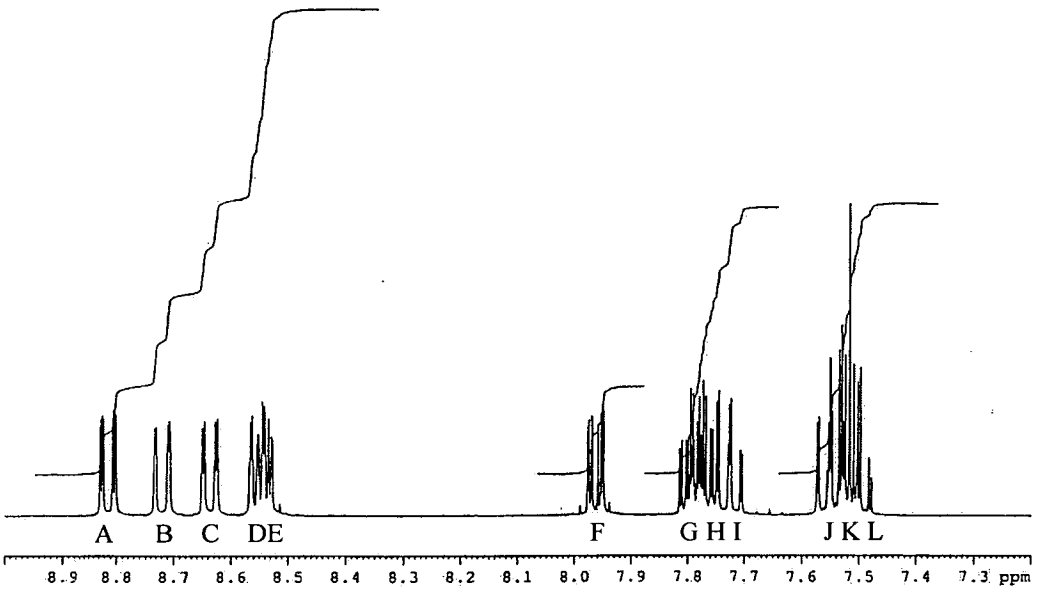


Figure 61

TOCSY spectrum of compound **450**.

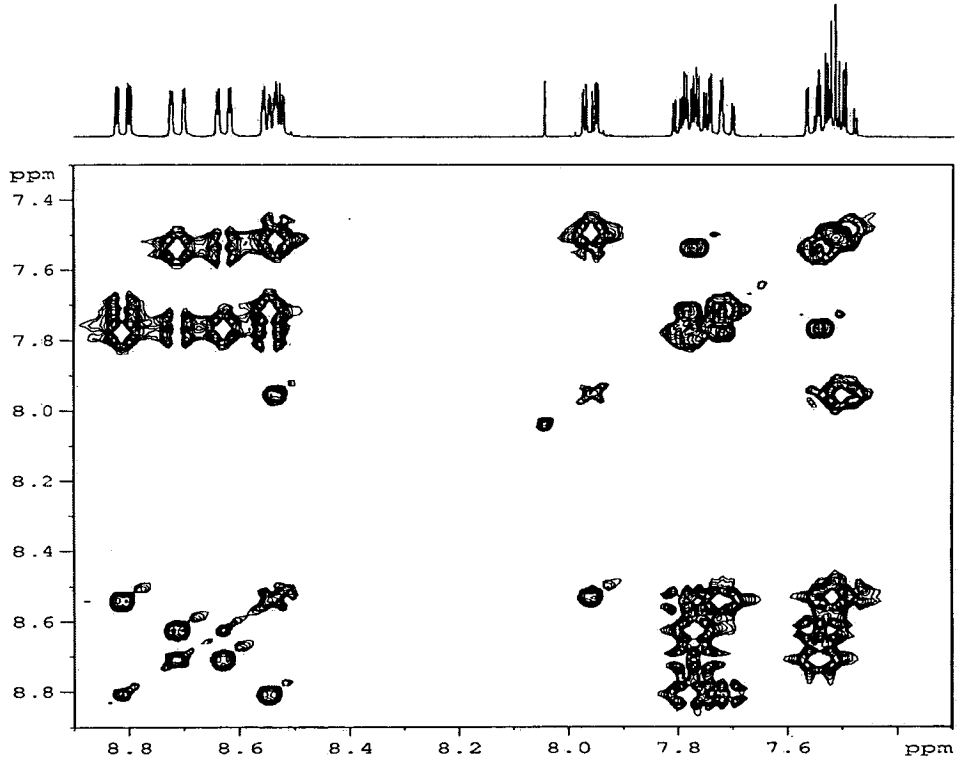


Figure 62

NOESY spectrum of compound **450**.

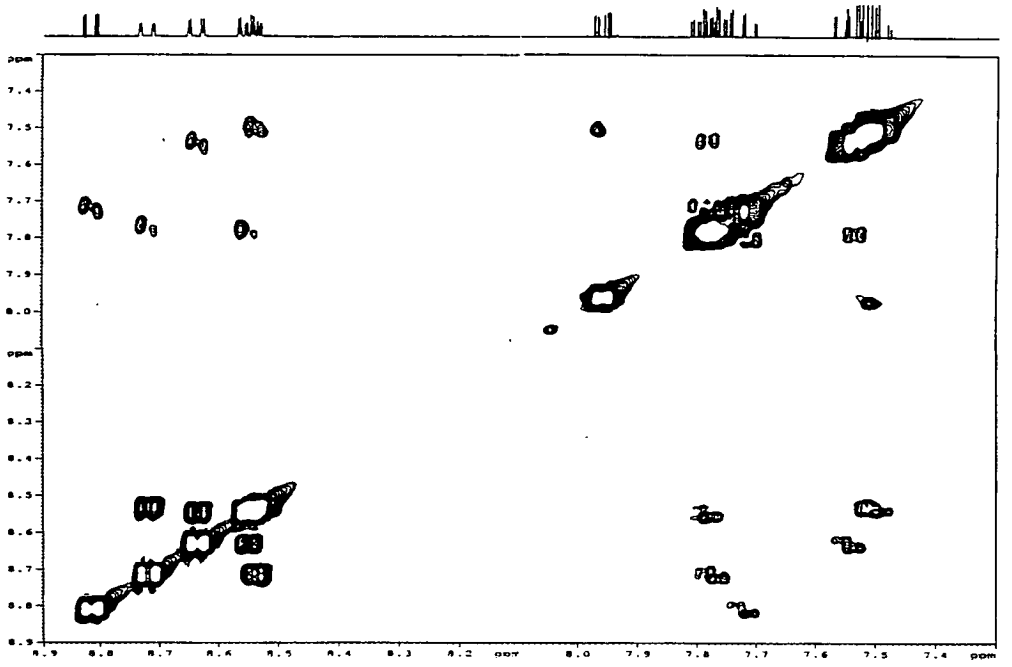


Figure 63

Proton-carbon Correlation spectrum for compound **450**.

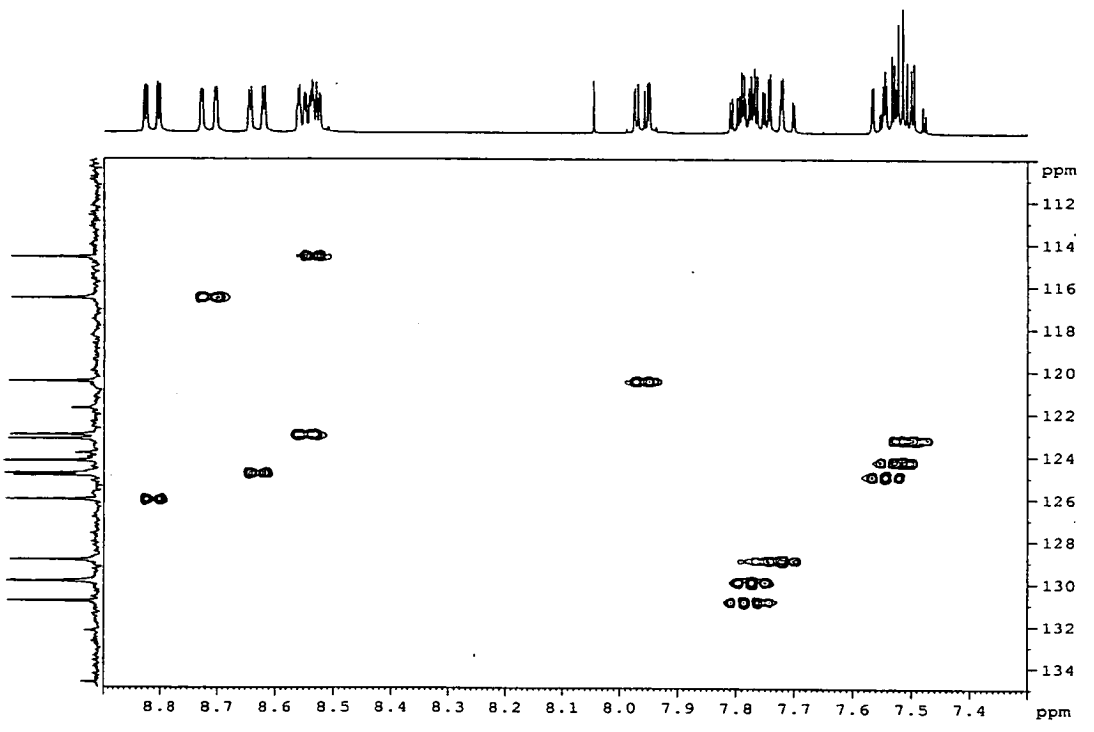
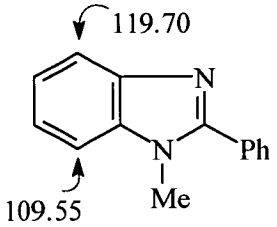


Figure 65

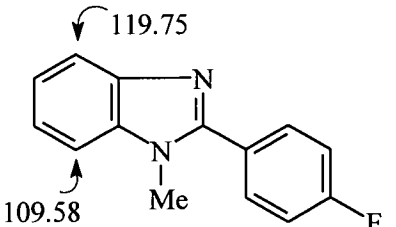
Proton	Associated carbon /ppm
A	126.09
B	116.60
C	124.86
D	123.06
E	114.65
F	120.54
G	130.91
H	129.98
I	128.96
J	124.96
K	124.27
L	123.25

Table 45:- ^{13}C NMR assignments for compound **450**.

The chemical shifts of the carbons associated with protons B and E are substantially deshielded, δ_C< 120ppm, which would correlate with carbons in the *ortho* position to a nitrogen with a lone pair. For example, the chemical shift of the *ortho* protons in aniline is 113 ppm.[81] Proton F is associated with a carbon of chemical shift of 121 ppm. This corresponds with the values for *N*-substituted benzimidazoles **485** and **486**, where this carbon has a chemical shift of ~120 ppm, as shown in **Figure 66**.



485



486

Figure 66

The chemical shift of the protons in the 4-position of benzimidazole is approximately 7.90ppm which would correspond with proton F being in this position in compound **350**. This is evidence which suggests that the assignment is as in **Figure 64(a)**. If it was as in **Figure 64(b)**, the chemical shifts of the B and E carbons would be difficult to rationalise when their positions are remote from the nitrogen atoms.

A COSY spectrum was obtained to assign the other protons and is shown in **Figure 67**. This shows unambiguously that proton A couples to proton I, proton B couples to proton H, proton C couples to proton J, proton D couples to proton G,

COSY spectrum for compound **450**.

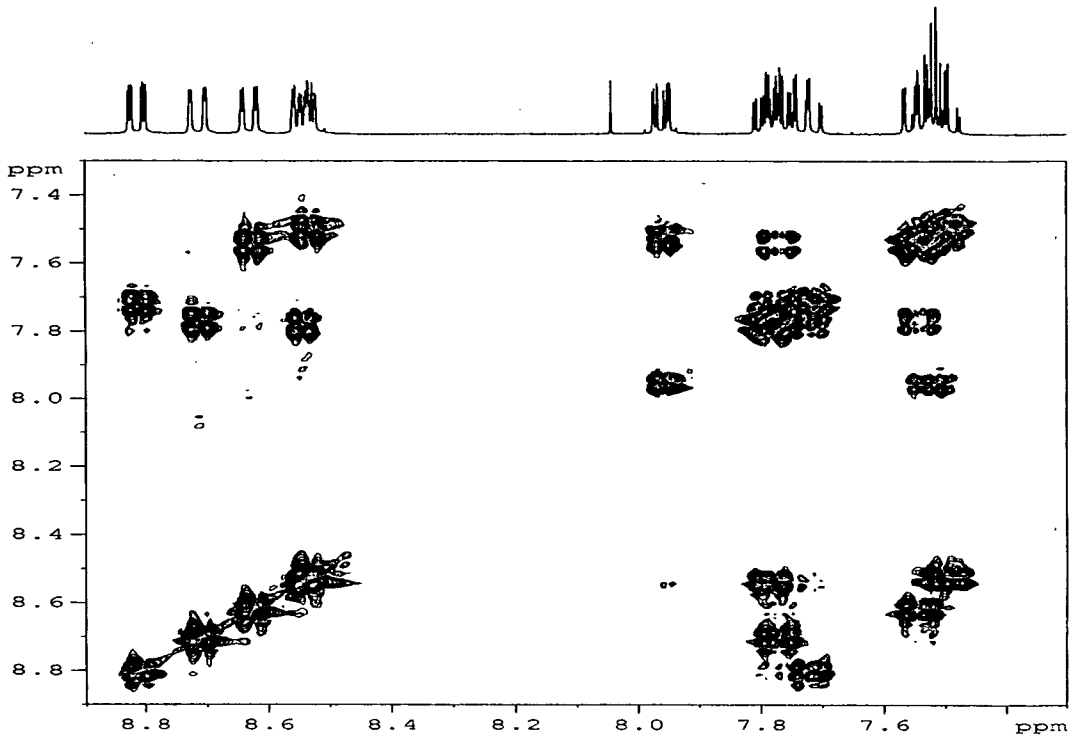


Figure 67

HMBC spectrum for compound **450**.

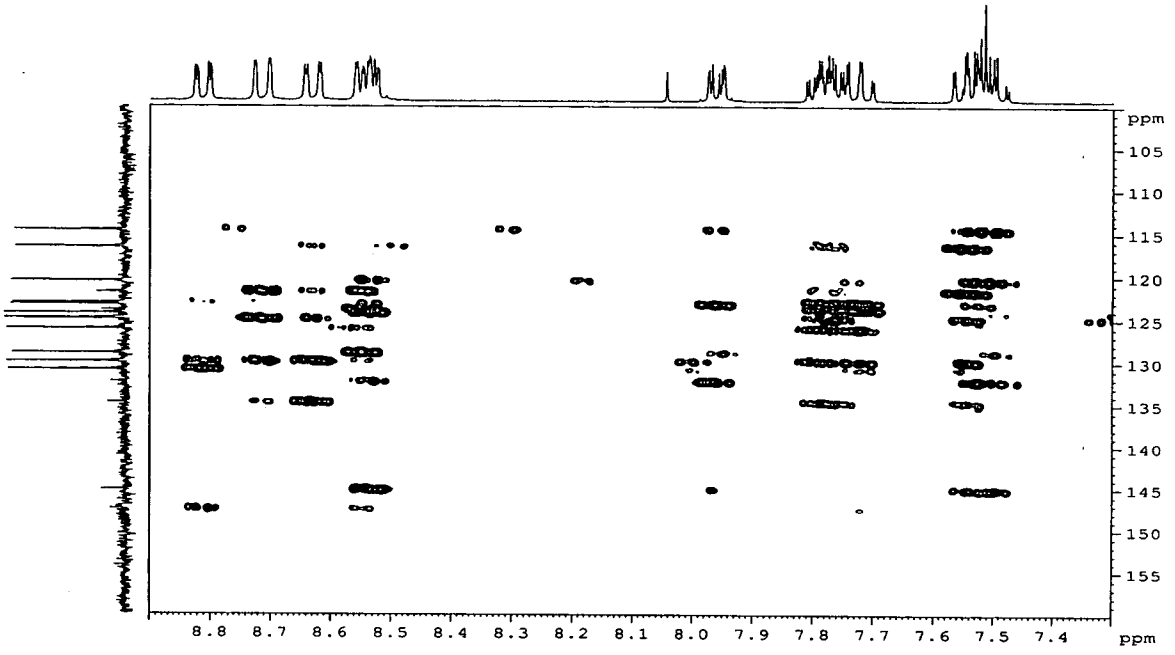


Figure 68

proton E couples to proton L and proton F couples to proton K. This is illustrated in **Figure 64(a)**.

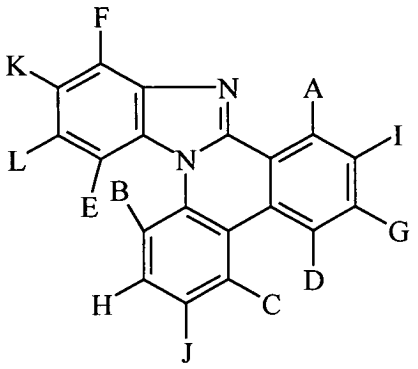


Figure 64(a)

The quaternaries for this compound occur at 147.50, 145.20, 134.76, 132.30, 129.92, 123.91 and 121.81 ppm. In order to assign these quaternaries, a HMBC experiment was carried out and its spectrum is shown in **Figure 68**. The quaternaries are labelled as shown in **Figure 69**.

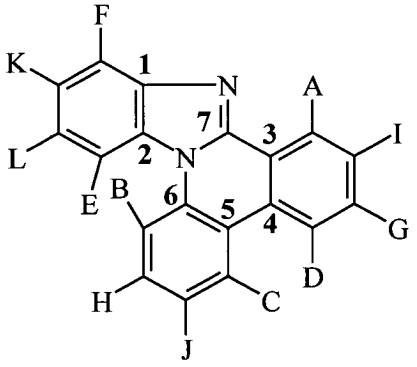


Figure 69

The quaternary at 147.50 ppm only shows one three bond coupling. This is to proton A suggesting that it must occur at position **7**. The quaternary at 145.20 ppm shows coupling to proton E, and to one of J/K/L suggesting that it must occur at position **1**. The quaternary at 134.76 ppm shows couplings to proton C and one of G/H/I suggesting that it is in position **6**. The quaternary at 132.30 ppm shows couplings to proton F, and one of J/K/L suggesting that it is in position **2**. The quaternary at 121.81 ppm shows couplings to proton B, proton D and one of J/K/L suggesting that it is in position **5**. The quaternary at 123.91 ppm shows couplings to proton D and one of G/H/I suggesting that it is in position **3**. The quaternary at 129.92 ppm shows couplings to proton A and one of G/H/I suggesting that it is in position **4**. The full assignment of this compound is shown in **Figure 70**.

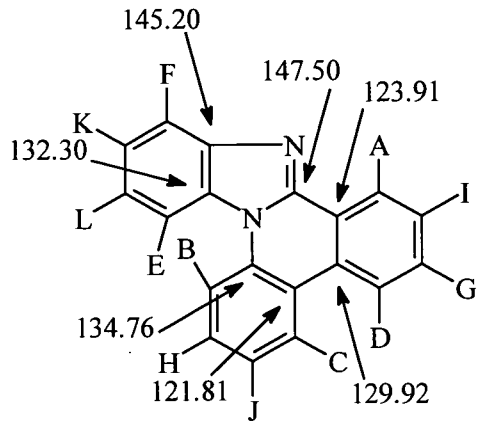


Figure 70

This chapter shows that 1-(2-nitrophenyl) substituted heterocycles are a source of aryl radicals in flash vacuum pyrolysis reactions. This route is synthetically versatile and in optimum cases provides a two-step route to pyrrolo[3,2,1-*jk*]carbazoles and indolo[3,2,1-*jk*]carbazole.

In some cases the reaction path was diverted to other products. Thus, when the corresponding benzimidazole and indazole systems were pyrolysed, the expected tetracycle rearranged under the reaction conditions to give 1-cyanocarbazole as the only product. FVP of the corresponding 2-methylbenzimidazole and indole systems gave 10*H*-4b,9-diazaindeno[1,2-*a*]indene and 10*H*-indolo[1,2-*a*]indole respectively. The mechanism for this reaction is thought to involve hydrogen transfers. However, this mechanism has not been fully elucidated. Cyclisation of the 2-(2-phenylbenzimidazol-1-yl)phenyl radical took place on the 2-phenyl substituent to give benzo[4,5]imidazo[1,2-*f*]phenanthridine rather than 1-phenyl-2,9b-diazacyclopenta[*jk*]fluorene.

4. REFERENCES.

3. EXPERIMENTAL.

7.1 ABBREVIATIONS.

NMR	nuclear magnetic resonance
δ_H, δ_C	chemical shift
p.p.m.	parts per million
FAB	fast atom bombardment
DMSO	dimethyl sulfoxide
DCM	dichloromethane
DMF	dimethylformamide
THF	tetrahydrofuran
FVP	flash vacuum pyrolysis
mol	moles
mmol	millimoles
M	molarity
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
q	quartet (^{1}H spectra)
m	multiplet
br	broad
J	coupling constant
quat	quaternary (^{13}C spectra)
mp	melting point
bp	boiling point
m/z	mass to charge ratio
$\mathbf{M^+}$	molecular ion mass
h	hours
min	minutes
T_f	furnace temperature
T_i	inlet temperature
t_m	time taken

m_a	mass of substrate used
P	pressure

7.2 INSTRUMENTATION AND GENERAL TECHNIQUES.

(a) Nuclear Magnetic Resonance Spectroscopy.

^{1}H NMR spectra were recorded on Bruker WH360 (360 MHz), Bruker AC250 (250 MHz), Bruker AC200 (200 MHz), and Varian Gemini 200 (200 MHz) spectrometers.

^{13}C NMR spectra were obtained on Bruker AC250 (63 MHz) and AC200 (50 MHz) instruments.

The Bruker WH360 was operated by Dr. D. Reed, the Bruker AC250 by Mr. J.R.A. Millar, the Bruker AC200 by Mr W.G. Kerr and the Varian Gemini 200 by Miss L. Crawford.

Spectra were recorded in [^{2}H] chloroform, unless otherwise stated. Chemical shifts (δ_H and δ_C) are quoted in ppm relative to tetramethylsilane, and all coupling constants are given in Hertz (Hz).

(b) Mass Spectrometry.

Low resolution electron impact mass spectra were recorded by Mr. H.G. McKenzie on a Finnigan 4600 instrument. High resolution and FAB mass spectra were obtained on a Kratos MS50 TC instrument operated by Mr. A.T. Taylor.
All spectra were obtained by electron impact instruments unless otherwise stated.

(c) Elemental Analysis.

Microanalyses were carried out on a Perkin Elmer 240 CHN Elemental Analyser by Mrs. L. Eades, Mr. S. Franklin and Mr. T. Calder.

(d) Structure Determination.

X-ray crystal structure data were obtained and solved by Dr. R.O. Gould and Dr. S. Parsons on a Stoe STADI-4 four circle diffractometer with graphite monochronator.

(e) Chromatography.

Thin-layer chromatography was carried out on precoated aluminium sheets (0.2mm silica gel, Merck, grade 60) impregnated with an ultra violet indicator.

Dry flash chromatography was carried out on silica gel (Merck, grade 60, 230-400 mesh, 60 Å). The crude materials were generally preabsorbed onto silica gel and then loaded onto the column. Ethyl acetate and *n*-hexane were frequently used as the solvent system with 10% increments in the polar component every two or three fractions.

(f) Solvents.

All solvents used were dried over molecular sieves or used without further purification.

(g) Infrared Spectroscopy.

IR spectra were obtained as liquid films or nujol mulls on a Perkin Elmer Paragon 1000 FT-IR spectrometer and are quoted in wavenumbers (cm^{-1}).

7.3 FLASH VACUUM PYROLYSIS.

Flash vacuum pyrolysis involves gaseous molecules being subjected to high temperatures for very short periods of time, usually 10^{-2}-10^{-3} seconds.

In principle, the substrate is distilled or sublimed through an electrically heated tube which is connected to a cold trap and vacuum line.

Figure 1 illustrates the apparatus used in such experiments and is based on the design of W.D. Crow of the Australian National University.

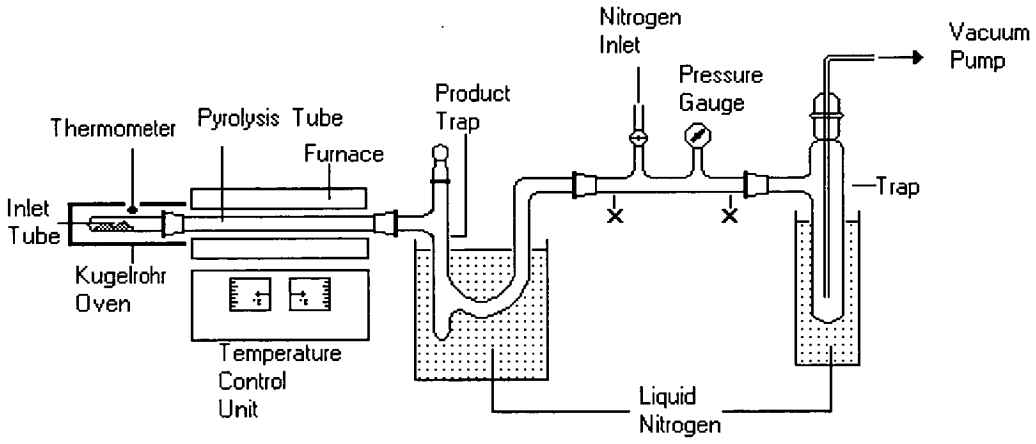


Figure 1

A glass Büchi oven was used to volatilise the substrate at temperatures lower than 300°C which is then drawn through a silica tube (30 × 2.5cm) heated by a Carbolite electronically controlled laboratory tube furnace Model No MTF 12/38/250. The products are collected at the exit of the furnace tube in a trap surrounded by liquid nitrogen. A "U-shaped" trap is used for small scale pyrolyses (up to 2g of substrate). The system was evacuated and the vacuum maintained by an Edwards Model ED100 high capacity oil pump. The entire pyrolysate was either scraped from the trap for analysis or washed through with a suitable solvent. For small scale pyrolyses (50 - 100 mg) the solvent of choice was frequently [^{2}H]chloroform enabling immediate examination by ^{1}H and ^{13}C NMR spectroscopy.

Standard pyrolysis parameters used throughout this section are furnace temperature T_f, inlet temperature T_i, pressure P, sublimation time t_m and mass of substrate m_a.

In some cases, alternative trapping methods were employed such as a cold finger trap (using dry ice/acetone as the cooling system) when the pyrolysis product was unstable and these are described where appropriate in the text.

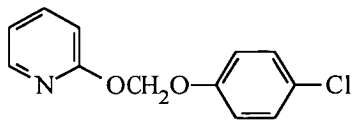
A. RADICAL RING EXPANSION REACTIONS.

7.4.1 Alkylation Reactions.

Method 1.

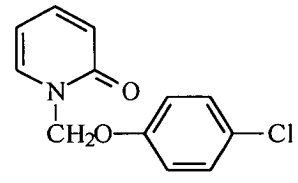
Powdered potassium hydroxide (2.24 g, 0.04 mol) was dissolved in DMSO (10 cm^3) and stirred for 5 min. The appropriate heterocycle (0.96 g, 10 mmol) was added and the solution was stirred for 45 min. α,4-Dichloroanisole (1.75 g, 10 mmol) was added and the solution was stirred for a further 45 min. It was then poured into water (40 cm^3) and extracted with ether (2 × 40 cm^3). The organic layer was washed with water (2 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting mixture was separated using dry flash chromatography on silica using hexane : ethyl acetate (1:1) as eluant. The heterocycle used is reported.

2-(*p*-chlorophenoxymethoxy)-pyridine 253.



[1*H*-pyridin-2-one-eluted first from column] (20%) bp 105 - 107 °C (0.8 Torr) (Found: M^+, 237.0376 and 235.0411. $C_{12}H_{10}{}^{37}ClNO_2$ and $C_{12}H_{10}{}^{35}ClNO_2$ require *M*, 237.0371 and 235.0400 respectively); ν_{max} (nujol) 1637.3 cm^{-1} (C=C aromatic); δ_H (250 MHz) 8.21 (1H, m), 7.61 (1H, m), 7.20 – 7.26 (2H, m), 6.93 – 7.08 (3H, m), 6.76 (1H, dd, ^3J 8.4, ^4J 0.8) and 6.05 (2H, s); δ_C (63 MHz) 161.68 (quat), 155.84 (quat), 146.96 (CH), 139.15 (CH), 129.28 (2 × CH), 127.19 (quat), 118.14 (CH), 117.56 (2 × CH), 111.30 (CH) and 87.38 (CH_2); *m/z* 237, 235 (M^+, 4 and 8%), 141 (59), 108 (99), 79 (55) and 78 (100).

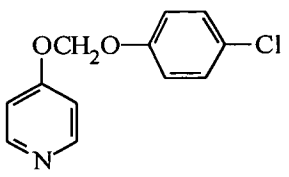
***N*-(*p*-chlorophenoxymethyl)-pyridin-2-one 252.**



[1*H*-pyridin-2-one-eluted second from column] (31%) mp 64 – 65 °C (from light petroleum) (Found: C, 61.25; H, 4.25; N, 6.0, $C_{12}H_{10}ClNO_2$ requires C, 61.15; H, 4.25; N, 5.95%); (Found: M^+, 237.0372 and 235.0391. $C_{12}H_{10}{}^{37}ClNO_2$ and $C_{12}H_{10}{}^{35}ClNO_2$ require *M*, 237.0371 and 235.0400 respectively); ν_{max} (nujol) 1663.7 cm^{-1} (C=O); δ_H (250 MHz) 7.18 – 7.42 (4H, m), 6.94 - 7.00 (2H, m), 6.55 (1H, ddd, ^3J 8.6, ^4J 1.4, ^5J 0.8), 6.18 (1H, td, ^3J 6.8, ^4J 1.4) and 5.86 (2H, s); δ_C (63 MHz) 162.01 (quat), 154.31 (quat), 140.08 (CH), 135.20 (CH), 129.54 (2 ×

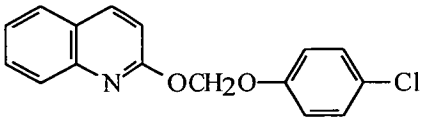
CH), 127.51 (quat), 121.37 (CH), 116.99 (2 × CH), 106.62 (CH) and 73.55 (CH_2); *m/z* 237, 235 (M^+, 0.5 and 1%), 141 (45), 96 (78) and 80 (100).

4-(*p*-chlorophenoxymethoxy)-pyridine 255.



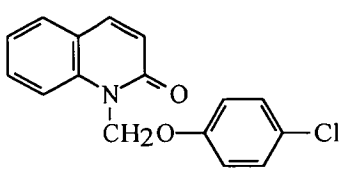
[1*H*-pyridin-4-one-only isomer eluted from column] (43%) mp 39 - 40 °C (from hexane and ethyl acetate) (Found: C, 57.9; H, 4.85; N, 5.15. $C_{12}H_{10}ClNO_2$ requires C, 57.85; H, 4.65; N, 5.65%); (Found: M^+, 235.0400. $C_{12}H_{10}{}^{35}ClNO_2$ requires *M*, 235.0400); ν_{max} (nujol) 1616.2 cm^{-1} (C=C aromatic); δ_H ([$^2H_6$]acetone) (250 MHz) 8.43 – 8.49 (2H, dd, ^3J 5.7, ^4J 1.5), 7.32 - 7.38 (2H, m), 7.08 – 7.18 (4H, m) and 5.96 (2H, s); δ_C ([$^2H_6$]acetone) (63 MHz) 161.68 (quat), 154.50 (quat), 150.39 (2 × CH), 128.59 (2 × CH), 126.28 (quat), 117.09 (2 × CH), 110.42 (2 × CH) and 88.84 (CH_2); *m/z* 237, 235 (M^+, 21 and 33%), 141 (34), 108 (69), 78 (91) and 51 (100).

2-(*p*-chlorophenoxymethoxy)-quinoline 257.



[1*H*-quinolin-2-one-eluted first from column] (32%) mp 66 - 68 °C (from hexane) (Found: C, 67.35; H, 4.15; N, 4.85. $C_{16}H_{12}ClNO_2$ requires C, 67.25; H, 4.2; N, 4.9%); ν_{max} (nujol) 1618.5 cm^{-1} (C=C aromatic); δ_H (250 MHz) 8.04 (1H, d, ^3J 8.8), 7.88 (1H, dd, ^3J 8.5, ^4J 1.5), 7.73 (1H, dd, ^3J 8.0, ^4J 1.3), 7.65 (1H, ddd, ^3J 8.5, ^3J 6.9, ^4J 1.3), 7.42 (1H, ddd, ^3J 8.0, ^3J 6.9, ^4J 1.3), 7.22 – 7.49 (4H, m), 6.94 (1H, d, ^3J 8.8) and 6.24 (2H, s); δ_C (63 MHz) 159.84 (quat), 155.87 (quat), 145.98 (quat), 139.43 (CH), 127.31 (quat), 129.67 (CH), 129.29 (2 × CH), 127.45 (CH), 127.34 (CH), 127.31 (quat), 125.45 (quat), 124.56 (CH), 117.57 (2 × CH), 112.57 (CH) and 87.48 (CH_2); *m/z* 287, 285 (M^+, 17 and 53%), 158 (100), 129 (67), 128 (99), 111 (45) and 77 (31).

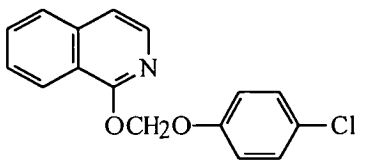
***N*-(*p*-chlorophenoxymethyl)-quinolin-2-one 256.**



[1*H*-quinolin-2-one-eluted second from column] (38%) mp 94 - 96 °C (from hexane) (Found: C, 67.45; H, 4.25; N, 4.85. $C_{16}H_{12}ClNO_2$ requires C, 67.25; H, 4.2; N, 4.9%); ν_{max} (nujol) 1680.1 cm^{-1} (C=O); δ_H (250 MHz) 7.64 (1H, d, ^3J 9.5), 7.49 – 7.58 (3H, m), 7.17 – 7.27 (3H, m), 7.03 – 7.08 (2H,

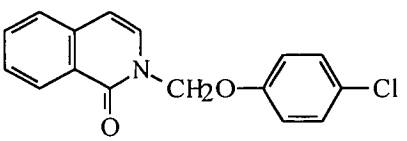
m), 6.62 (1H, d, ^3J 9.5) and 6.26 (2H, s); δ_C (63 MHz) 161.78 (quat), 154.44 (quat), 140.46 (CH), 138.58 (quat), 130.76 (CH), 129.30 (2 × CH), 128.66 (CH), 127.05 (quat), 122.89 (CH), 121.14 (CH), 120.55 (quat), 117.16 (2 × CH), 114.92 (CH) and 69.65 (CH_2); *m/z* 287, 285 (M^+, 6 and 18%), 158 (100), 128 (76) and 82 (40).

1-(*p*-chlorophenoxymethoxy)-isoquinoline 259.



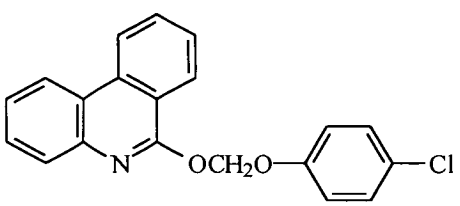
[2*H*-isoquinolin-1-one-eluted first from column] (21%) mp 78 - 79 °C (from hexane) (Found: C, 67.3; H, 4.25; N, 5.05. $C_{16}H_{12}ClNO_2$ requires C, 67.35; H, 4.2; N, 4.9%); ν_{max} (nujol) 1617.4 cm^{-1} (C=C aromatic); δ_H (250 MHz) 8.22 (1H, m), 8.04 (1H, m), 7.51 – 7.74 (3H, m), 7.03 – 7.32 (5H, m) and 6.27 (2H, s); δ_C (63 MHz) 156.01 (quat), 139.35 (CH), 138.52 (quat), 130.66 (CH), 129.36 (2 × CH), 127.36 (quat), 126.90 (CH), 126.14 (CH), 123.81 (CH), 119.52 (quat), 118.92 (quat), 117.65 (2 × CH), 116.17 (CH) and 87.79 (CH_2); *m/z* (FAB +ve) 288, 286 (M^+, 32 and 100%), 281 (19), 255 (13), 158 (67), 148 (19), 141 (25), 128 (23) and 73 (29).

***N*-(*p*-chlorophenoxymethyl)-isoquinolin-1-one 258.**



[2*H*-isoquinolin-1-one-eluted second from column] (48%) mp 133 - 135 °C (from cyclohexane) (Found: C, 67.6; H, 4.5; N, 4.65. $C_{16}H_{12}ClNO_2$ requires C, 67.35; H, 4.2; N, 4.9%); ν_{max} (nujol) 1659.9 cm^{-1} (C=O); δ_H (250 MHz) 8.41 (1H, d, ^3J 7.4), 7.43 – 7.67 (3H, m), 7.18 – 7.25 (3H, m), 6.99 – 7.04 (2H, m), 6.52 (1H, d, ^3J 7.4) and 5.96 (2H, s); δ_C (63 MHz) 161.86 (quat), 154.56 (quat), 136.76 (quat), 132.73 (CH), 129.45 (2 × CH), 129.13 (CH), 128.06 (CH), 127.29 (quat), 127.10 (CH), 125.96 (CH), 117.95 (quat), 117.65 (2 × CH), 116.17 (CH) and 87.79 (CH_2); *m/z* 287, 285 (M^+, 5 and 16%), 241 (3), 158 (100), 128 (85), 103 (14) and 77 (31).

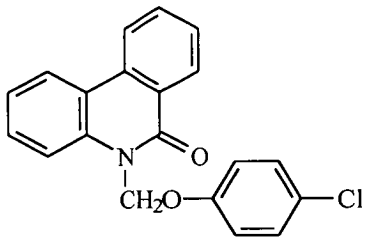
6-(*p*-chlorophenoxymethoxy)-phenanthridine 261.



[5*H*-phenanthridin-6-one-eluted first from column] (24%) mp 245 - 247 °C (Found: C, 70.45; H, 4.2; N, 3.95. $C_{20}H_{14}ClNO_2.0.3H_2O$ requires C, 70.5; H, 4.1; N, 4.15%); (Found:

M^+, 337.0699 and 335.0707. $C_{20}H_{14}{}^{37}ClNO_2$ and $C_{20}H_{14}{}^{35}ClNO_2$ require *M*, 337.0684 and 335.0713 respectively); ν_{max} (nujol) 1616.7 cm^{-1} (C=C aomatic); δ_H (250 MHz) 8.50 (1H, dd, ^3J 8.0, ^4J 1.4), 8.20 – 8.24 (2H, m), 7.05 – 7.78 (9H, m) and 6.36 (2H, s); δ_C (63 MHz) 161.50 (quat), 154.68 (quat), 136.41 (quat), 133.90 (quat), 133.07 (CH), 129.61 (CH), 129.37 (2 × CH), 129.13 (CH), 128.00 (CH), 127.08 (quat), 124.77 (quat), 123.23 (CH), 123.13 (CH), 121.62 (CH), 119.24 (quat), 117.35 (2 × CH), 115.84 (CH) and 70.42 (CH_2); *m/z* 337, 335 (M^+, 3 and 7%), 270 (21), 268 (27), 208 (48), 178 (43), 152 (15), 141 (60), 128 (100), 98 (41) and 75 (49).

N-(*p*-chlorophenoxymethyl)-phenanthridin-6-one 260.



[5*H*-phenanthridin-6-one-eluted second from column] (32%) mp 192 - 193 °C (Found: C, 69.0; H, 3.85; N, 4.0. $C_{20}H_{14}ClNO_2.0.7H_2O$ requires C, 69.05; H, 4.0; N, 4.2%); ν_{max} (nujol) 1650.3 cm^{-1} (C=O); (Found: M^+, 338.0760 and 336.0791. $C_{20}H_{14}{}^{37}ClNO_2$ and $C_{20}H_{14}{}^{35}ClNO_2$ require *M*, 338.0762 and 336.0791 respectively) δ_H (250 MHz) 8.49 (1H, d, ^3J 8.2), 8.42 (1H, dd, ^3J 8.0 ^4J 1.4), 8.31 (1H, m), 6.98 – 7.94 (9H, m) and 6.41 (2H, s); δ_C (63 MHz) 156.64 (quat), 155.98 (quat), 155.19 (quat), 142.42 (quat), 134.94 (quat), 131.07 (CH), 129.35 (2 × CH), 128.77 (CH), 128.00 (CH), 127.29 (CH), 124.92 (CH), 124.71 (CH), 122.67 (quat), 121.98 (CH), 121.83 (CH), 119.32 (quat), 117.58 (2 × CH) and 87.78 (CH_2); *m/z* (FAB +ve) 338, 336 (M^+, 10 and 38%), 308 (11), 208 (10), 147 (12), 136 (100) and 73 (94).

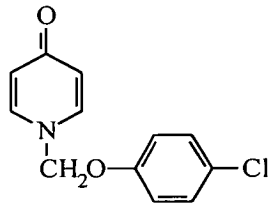
Method 2.

The appropriate heterocycle (10 mmol) was dissolved in THF (40 cm^3) under dry nitrogen. Sodium hydride (3 × excess) was added and the mixture was allowed to stir for 5 min. α,4-Dichloroanisole (1.75 g, 10 mmol) was added and the solution was heated under reflux for 2 h. It was allowed to cool and the solvent removed under reduced pressure. Ethanol (10 cm^3) was added dropwise and then the solution was added to water (100 cm^3) and extracted with DCM (3 × 50 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting

mixture was separated using dry flash chromatography on silica with ethyl acetate as eluant. The heterocycle used is reported.

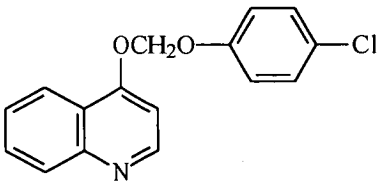
4-(*p*-chlorophenoxymethoxy)-pyridine 255. [1*H*-pyridin-4-one-eluted first from column] (12%) mp 39 - 40°C (from hexane and ethyl acetate); [as above]

***N*-(*p*-chlorophenoxymethyl)-pyridin-4-one 254.**



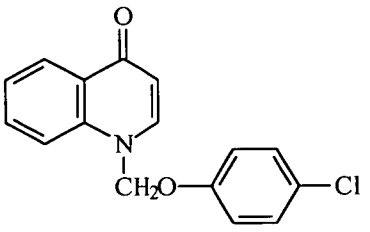
[1*H*-pyridin-4-one-eluted second from column] (35%) mp 148 - 149 °C (from toluene) (Found: C, 61.0; H, 4.3; N, 5.95. $C_{12}H_{10}ClNO_2$ requires C, 61.15; H, 4.25; N, 5.95%); (Found: M^+, 237.0361 and 235.0405. $C_{12}H_{10}{}^{37}ClNO_2$ and $C_{12}H_{10}{}^{35}ClNO_2$ require *M*, 237.0371 and 235.0400 respectively); ν_{max} (nujol) 1640.3 cm^{-1} (C=O); δ_H (250 MHz) 7.33 - 7.40 (2H, m, ^3J 6.0), 7.23 – 7.29 (2H, m, ^3J 6.8), 6.79 - 6.86 (2H, m, ^3J 6.8), 6.32 – 6.36 (2H, m, ^3J 6.0) and 5.49 (2H, s); δ_C (63 MHz) 179.26 (quat), 153.97 (quat), 139.02 (2 × CH), 129.97 (2 × CH), 129.19 (quat), 118.78 (4 × CH) [2 peaks superimposed] and 83.53 (CH_2); *m/z* 237, 235 (M^+, 1 and 3%), 108 (100) and 82 (40).

4-(*p*-chlorophenoxymethoxy)-quinoline 263.



[1*H*-quinolin-4-one-eluted first from column] (15%) mp 203 - 204 °C (from hexane) (Found: C, 66.85; H, 4.05; N, 4.95. $C_{16}H_{12}ClNO_2$ requires C, 67.25; H, 4.2; N, 4.9%); (Found: M^+, 287.0515 and 285.0550. $C_{16}H_{12}{}^{37}ClNO_2$ and $C_{16}H_{12}{}^{35}ClNO_2$ require *M*, 287.0527 and 285.0557 respectively); ν_{max} (nujol) 1619.2 cm^{-1} (C=C aromatic); δ_H (250 MHz) 8.78 (1H, d, ^3J 5.2), 8.17 (1H, ddd, ^3J 8.4, ^4J 1.5, ^5J 0.6), 8.04 (1H, ddd, ^3J 8.6, ^4J 1.3, ^5J 0.6), 7.70 (1H, ddd, ^3J 8.4 6.9, ^4J 1.5), 7.50 (1H, ddd, ^3J 9.2, 7.9 ^4J 1.3), 7.03 – 7.28 (5H, m) and 5.93 (2H, s); δ_C (63 MHz) 159.06 (quat), 155.05 (quat), 151.03 (CH), 149.31 (quat), 129.84 (CH), 129.51 (2 × CH), 128.93 (CH), 128.03 (quat), 125.93 (CH), 121.45 (CH), 121.05 (quat), 117.72 (2 × CH), 102.82 (CH) and 90.45 (CH_2); *m/z* 287, 285 (M^+, 3 and 6%), 158 (100), 132 (21), 130 (22) and 77 (22).

***N*-(*p*-chlorophenoxymethyl)-quinolin-4-one 262.**



[1*H*-quinolin-4-one-eluted second from column] (66%) mp 205 – 206 °C (from hexane) (Found: C, 66.55; H, 4.15; N, 4.85. $C_{16}H_{12}ClNO_2$ requires C, 67.25; H, 4.2; N, 4.9%); (Found: M^+, 287.0571 and 285.0588. $C_{16}H_{12}{}^{37}ClNO_2$ and $C_{16}H_{12}{}^{35}ClNO_2$ require *M*, 287.0527 and 285.0557 respectively); ν_{max} (nujol) 1620.1 cm^{-1} (C=O); δ_H (250 MHz) 8.40 (1H, dd, ^3J 8.1, ^4J 1.7), 7.67 (1H, ddd, ^3J 8.5, ^3J 6.9), 7.55 (1H, d, ^3J 8.1), 7.47 (1H, d, ^3J 7.8), 7.40 (1H, dd, ^3J 6.9, ^4J 1.7), 7.22 – 7.29 (2H, m), 6.81 – 6.87 (2H, m), 6.16 (1H, d, ^3J 7.8) and 5.86 (2H, s); δ_C (63 MHz) 178.49 (quat), 154.23 (quat), 142.45 (CH), 139.46 (quat), 132.48 (CH), 129.88 (2 × CH), 128.86 (quat), 126.84 (CH), 126.70 (quat), 124.34 (CH), 118.76 (2 × CH), 115.62 (CH), 110.38 (CH) and 81.26 (CH_2); *m/z* 287, 285 (M^+, 3 and 8%), 158 (100), 141 (39), 128 (58), 111 (35), 101 (22) and 77(8).

7.4.2 Pyrolysis of *N*-(*p*-chlorophenoxymethyl)-substituted heterocycles and the 4- and 2-(*p*-chlorophenoxymethoxy)-pyridines.

The appropriate derivative was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent to enable removal from the trap. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets. (The yields for the experiments marked with an * were estimated by the introduction of a known amount of cyclohexane into the sample, otherwise dry flash chromatography on silica was carried out using hexane : ethyl acetate as eluant).

***4-(*p*-chlorophenoxymethoxy)-pyridine.** [T_f 750 °C, T_i 150 °C, *P* 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced *p*-chlorophenol[81] **235** (84%) δ_H (250 MHz) 7.03 - 7.10 (2H, m, ^3J 8.8) and 6.75 – 6.73 (2H, m, ^3J 8.8); δ_C (63 MHz) 155.52 (quat), 129.04 (2 × CH), 123.96 (quat) and 116.71 (2 × CH). *p*-chlorobenzaldehyde[81] **297** (7%) δ_H (250 MHz) 9.92 (1H, s), 7.77 (2H, d, ^3J 8.2) and 7.45 (2H, d, ^3J 8.2); δ_C (63 MHz) 190.95 (CH),

140.33 (quat), 137.71 (quat), 130.70 (2 × CH) and 129.21 (2 × CH). 4-pyridinecarboxaldehyde[81] **296** (40%) δ_H (250 MHz) 10.04 (1H, s), 8.82 (2H, d, ^3J 5.8) and 7.70 (2H, d, ^3J 5.8); δ_C (63 MHz) 191.14 (CH), 150.46 (2 × CH), 141.49 (quat) and 122.29 (2 × CH).

***2-(*p*-chlorophenoxymethoxy)-pyridine.** [T_f 750 °C, T_i 120 °C, P 0.002 Torr, t_m 30 min, m_a 0.15 g]

Pyrolysis produced *p*-chlorophenol[81] **235** (69%) δ_H (250 MHz) 7.05 – 7.15 (2H, m, ^3J 8.8) and 6.70 – 6.75 (2H, m, ^3J 8.8); δ_C (63 MHz) 155.34 (quat), 129.14 (2 × CH), 124.25 (quat) and 116.70 (2 × CH). 1*H*-pyridin-2-one[81] **278** (84%) δ_H (250 MHz) 7.36 – 7.45 (2H, m), 6.52 (1H, d, ^3J 9.1) and 6.24 (1H, t, ^3J 6.6); δ_C (63 MHz) 164.89 (quat), 142.29 (CH), 134.64 (CH), 119.71 (CH) and 107.79 (CH).

***N*-(*p*-chlorophenoxymethyl)-pyridin-2-one** [T_f 750 °C, T_i 150 °C, P 0.003 Torr, t_m 30 min, m_a 0.20 g].

Pyrolysis produced *p*-chlorophenol[81] **235** (73%) δ_H (250 MHz) 7.05 – 7.13 (2H, m, ^3J 8.9) and 6.77 – 6.93 (2H, m, ^3J 8.9); δ_C (63 MHz) 155.34 (quat), 129.14 (2 × CH), 124.25 (quat) and 116.70 (2 × CH). 1*H*-pyridin-2-one[81] **278** (86%) δ_H (250 MHz) 7.37 - 7.55 (2H, m), 6.62 (1H, d, ^3J 9.1) and 6.34 (1H, ddt, ^3J 6.6, ^3J 6.6 and ^4J 1.0); δ_C (63 MHz) 164.89 (quat), 142.29 (CH), 134.64 (CH), 119.71 (CH) and 107.79 (CH).

***N*-(*p*-chlorophenoxymethyl)-pyridin-4-one** [T_f 750 °C, T_i 120 °C, P 0.005 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced pyridine[81] **240** (44%) δ_H (250 MHz) 8.59 - 8.62 (2H, m), 7.86 (1H, m) and 7.42 – 7.47 (2H, m); δ_C 147.43 (2 × CH), 138.32 (CH) and 124.67 (2 × CH). *p*-chlorophenol[81] **235** (82%) δ_H (250 MHz) 7.09 – 7.14 (2H, m, ^3J 8.8) and 6.75 – 6.84 (2H, m, ^3J 8.8); δ_C (63 MHz) 155.20 (quat), 129.20 (2 × CH), 124.47 (quat) and 116.76 (2 × CH).

***N*-(*p*-chlorophenoxymethyl)-quinolin-2-one** [T_f 750 °C, T_i 120 °C, P 0.002 Torr, t_m 20 min, m_a 0.30 g]

Pyrolysis produced *p*-chlorophenol[81] **235** (80%) δ_H (250 MHz) 7.15 – 7.18 (2H, m, ^3J 8.8) and 6.73 – 6.78 (2H, m, ^3J 8.8); δ_C (63 MHz) 154.10 (quat), 129.39 (2 × CH), 125.44 (quat) and 116.56 (2 × CH); isoquinoline[81] **268** (22%) δ_H (250 MHz) 9.28

(1H, br), 8.50 (1H, d, ^3J 5.7) and 7.39 – 7.96 (5H, m); δ_C (63 MHz) 151.28 (CH), 141.25 (CH), 136.94 (quat), 131.17 (CH), 129.39 (quat), 127.91 (CH), 127.82 (CH), 126.48 (CH) and 121.34 (quat); 1*H*-quinolin-2-one[158] **275** (54%) δ_H (250 MHz) 7.82 (1H, d, ^3J 9.5), 7.56 (1H, d, ^3J 7.8), 7.47 – 7.53 (2H, m), 7.21 (1H, t, ^3J 8.1) and 6.73 (1H, d, ^3J 9.5); δ_C (63 MHz) 164.66 (quat), 140.95 (CH), 138.41 (quat), 130.53 (CH), 127.57 (CH), 122.55 (CH), 122.16 (CH), 119.79 (quat) and 116.17 (CH).

***N*-(*p*-chlorophenoxymethyl)-quinolin-4-one** [T_f 750 °C, T_i 200 °C, P 0.002 Torr, t_m 35 min, m_a 0.5 g]

Pyrolysis produced *p*-chlorophenol[81] **235** (82%) δ_H (250 MHz) 7.07 – 7.10 (2H, m, ^3J 8.8) and 6.78 – 6.86 (2H, m, ^3J 8.8); δ_C (63 MHz) 155.52 (quat), 129.74 (2 × CH), 125.20 (quat) and 117.28 (2 × CH); isoquinoline[81] **268** (32%) δ_H (250 MHz) 9.24 (1H, s), 8.46 (1H, d, ^3J 5.8) and 7.44 - 7.88 (5H, m); δ_C (63 MHz) 151.71 (CH), 141.05 (CH), 136.76 (quat), 131.99 (CH), 129.03 (quat), 127.62 (CH), 127.06 (CH), 125.72 (CH) and 121.65 (quat); 1*H*-quinolin-4-one[158] **269** (39%) δ_H (250 MHz) 11.62 (1H, br), 8.38 (1H, dt, ^3J 8.2, ^4J 1.0), 7.76 (1H, d, ^3J 7.4), 7.30 – 7.66 (3H, m) and 6.32 (1H, d, ^3J 7.4); δ_C (63 MHz) 179.10 (quat), 140.08 (quat), 139.14 (CH), 132.06 (CH), 126.01 (quat), 125.49 (CH), 123.97 (CH), 118.36 (CH) and 109.26 (CH).

***N*-(*p*-chlorophenoxymethyl)-isoquinolin-1-one** [T_f 750 °C, T_i 140 - 170 °C, P 0.003 Torr, t_m 20 min, m_a 0.5 g]

Pyrolysis produced *p*-chlorophenol[81] **235** (77%) δ_H (250 MHz) 7.09 – 7.14 (2H, m, ^3J 8.8) and 6.77 – 6.83 (2H, m, ^3J 8.8); δ_C (63 MHz) 154.71 (quat), 129.26 (2 × CH), 124.91 (quat) and 116.65 (2 × CH); isocarbostyril[81] **285** (70%) δ_H (250 MHz) 11.84 (1H, br), 8.41 (1H, m), 7.47 – 7.70 (3H, m) 7.19 (1H, d, ^3J 7.2) and 6.57 (1H, d, ^3J 7.2); δ_C (63 MHz) 163.91 (quat), 138.01 (quat), 132.71 (CH), 127.27 (2 × CH), 126.87 (CH), 126.18 (CH), 125.83 (quat) and 106.95 (CH).

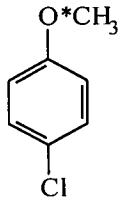
***N*-(*p*-chlorophenoxymethyl)-phenanthridin-6-one** [T_f 750 °C, T_i 200 °C, P 0.001 Torr, t_m 40 min, m_a 0.19 g]

Pyrolysis produced *p*-chlorophenol[81] **235** (77%) δ_H (250 MHz) 7.07 – 7.10 (2H, m, ^3J 8.8) and 6.78 – 6.86 (2H, m, ^3J 8.8); δ_C (63 MHz) 155.58 (quat), 129.87 (2 × CH), 123.76 (quat) and 117.31 (2 × CH); phenanthridine[81] **276** (42%) δ_H (250 MHz) 9.28 (1H, s), 8.59 – 8.64 (2H, m), 7.90 – 8.24 (2H, m) and 7.69 – 7.78 (4H, m); δ_C (63

MHz) 153.49 (CH), 143.49 (quat), 132.31 (quat), 130.14 (CH), 130.08 (CH), 128.31 (CH), 127.26 (CH), 126.80 (CH), 126.57 (CH), 125.92 (quat), 122.86 (quat), 122.43 (CH) and 122.15 (CH); 5*H*-phenanthridin-6-one[81] **277** (10%) δ_H (250 MHz) 8.53 (1H, dd, ^3J 8.5, ^4J 1.5), 8.30 (1H, d, ^3J 8.5), 8.21 (1H, dd, ^3J 8.0, ^4J 1.5), 7.80 (1H, td, ^3J 8.5, ^4J 1.5), 7.60 (1H, td, ^3J 8.5, ^4J 1.5), 7.46 (1H, td, ^3J 8.5, ^4J 1.5), 7.29 (1H, td, ^3J 8.0, ^4J 1.5) and 7.20 (1H, dd, ^3J 8.5, ^4J 1.5); δ_C (63 MHz) 160.69 (quat), 136.43 (quat), 134.12 (quat), 132.64 (CH), 129.43 (CH), 127.78 (CH), 127.35 (CH), 125.56 (quat), 123.10 (CH), 122.46 (CH), 122.12 (CH), 117.43 (quat) and 116.00 (CH).

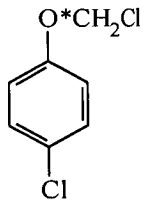
7.4.3 Synthesis of ^{13}C labelled compounds.

i/ Synthesis of [7-^{13}C]-*p*-chloroanisole.



p-Chlorophenol (1.29 g, 10 mmol) was dissolved in DMF (15 cm^3). Potassium carbonate (1.96 g, 14.2 mmol) and [^{13}C]iodomethane (99% incorporation, 1.00 g, 6.99 mmol) were added and the mixture was allowed to stir overnight at room temperature. The solution was added to 2M NaOH (30 cm^3) and extracted with ether (3 × 20 cm^3). The organic layer was washed with water (3 × 20 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the desired product which was used without further purification. [0.86 g, 85% (based on iodomethane)].

ii/ Synthesis of [7-^{13}C]-α,4-dichloroanisole.



[7-^{13}C]-*p*-Chloroanisole (0.86 g, 5.99 mmol) and phosphorus pentachloride (1.26 g, 6.04 mmol) were placed in a Kugelrohr and heated to 145 °C. The temperature was raised slowly to 155 °C so that a gentle reaction was maintained. Once bubbling had ceased, the temperature was raised to 165 °C for 5 min to distil over any remaining PCl_5. The residue left after this distillation was then fractionally distilled under water pump pressure to yield the desired [7-^{13}C]-α,4-dichloroanisole.(0.39 g, 36%) bp 110 – 112 °C (4 Torr), [lit.,[81] 122 °C (18 Torr)]

The contents of all the other bulbs were added to water (5 cm^3), extracted with DCM (2 × 5 cm^3). The organic layer was washed with water (2 × 5 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was purified was

Kugelrohr distillation to give *p*-chloroanisole (0.28 g) bp 85 - 86 °C (8 Torr), [lit.,[81] 200 °C] which was reacted as before.

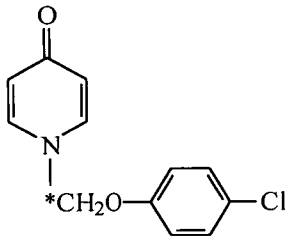
iii/ Synthesis of the ^{13}C-labelled *N*-(*p*-chlorophenoxymethyl)-pyridin-4-one.

The appropriate heterocycle (0.5 mmol) was dissolved in THF (10 cm^3) under dry nitrogen. Sodium hydride (3 × excess) was added and the mixture was allowed to stir for 5 min. The labelled α,4-dichloroanisole (0.5 mmol) was added and the solution was heated under reflux for 2 h. It was allowed to cool and the solvent removed under reduced pressure. Ethanol (10 cm^3) was added dropwise and then the solution was added to water (50 cm^3) and extracted with DCM (3 × 50 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting mixture was separated using dry flash chromatography on silica with ethyl acetate as eluant.

Labelled *N*-(*p*-chlorophenoxymethyl)-pyridin-4-one.

(30%) δ_H (250 MHz) 7.23 – 7.33 (4H, m), 6.79 – 6.86 (2H, m), 6.32 – 6.36 (2H, m) and 5.49 (2H, d, ^1J 164).

iv/ Pyrolysis of the ^{13}C-labelled *N*-(*p*-chlorophenoxymethyl)-pyridin-4-one.



[T_f 850 °C, T_i 750 °C, 120 °C, P 0.005 Torr, t_m 10 min, m_a 0.005 g] (Labelled product reported only)

δ_H (360 MHz) 8.64 (1H, m), 8.64 (1H, d, J 179.2), 7.75 – 7.81 (1H, m) and 7.33 – 7.41 (2H, m); δ_C (63 MHz) 148.90 (2 × CH) [position of ^{13}C label], 129.31 (CH), and 116.61 (2 × CH).

7.4.4 Decarbonylation of tropolone.

Tropolone was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent to enable removal from the trap. The pyrolysis parameters given in brackets.

[T_f 650 °C, T_i 180 - 200 °C, P 0.0085 Torr, t_m 15 min, m_a 0.05 g]

Pyrolysis produced tropolone (100%) δ_H (250 MHz) 7.24 - 7.41 (4H, m) and 6.97 - 7.04 (1H, m); δ_C (63 MHz) 171.65 (2 × quat), 137.57 (2 × CH), 128.16 (CH) and 123.79 (2 × CH).

[T_f 700 °C, T_i 180 - 200 °C, P 0.007 Torr, t_m 15 min, m_a 0.05 g]

Pyrolysis produced tropolone (87%) and phenol (13%) δ_H (250 MHz) 7.21 - 7.48 (2H, m) and 6.82 - 6.98 (3H, m); δ_C (63 MHz) 155.18 (quat), 129.56 (2 × CH), 120.70 (CH) and 115.20 (2 × CH).

[T_f 750 °C, T_i 180 - 200 °C, P 0.006 Torr, t_m 15 min, m_a 0.05 g]

Pyrolysis produced tropolone (60%) and phenol (40%).

[T_f 800 °C, T_i 180 - 200 °C, P 0.0065 Torr, t_m 15 min, m_a 0.05 g]

Pyrolysis produced tropolone (11%) and phenol (89%).

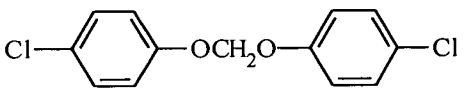
[T_f 850 °C, T_i 180 - 200 °C, P 0.008 Torr, t_m 15 min, m_a 0.05 g]

Pyrolysis produced phenol (100%).

7.4.5 Synthesis of other radical generators for mechanistic purposes.

p-Chlorophenol (0.73 g, 5.6 mmol) was dissolved in DMF (30 cm^3). Potassium carbonate (0.77 g, 5.6 mmol) and α,4-dichloroanisole (1.0 g, 5.6 mmol) were added and the solution was allowed to stir overnight at room temperature. The mixture was added to water (100 cm^3) and extracted using ether (3 × 100 cm^3). The organic layer was washed with water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

1-(1-chloro-4-phenoxymethoxy)-4-chlorobenzene 295.



(1.26 g, 84%) mp 73 – 75 °C (from hexane) (Found: C, 58.2; H, 3.85. $C_{13}H_{10}Cl_2O_2$ requires C, 58.0; H, 3.7%); δ_H (250 MHz) 6.98 - 7.28 (7H, m), 6.75 - 6.79 (1H, m) and 5.66 (2H, m); δ_C (63 MHz) 155.17 (2 × quat), 129.37 (4 × CH), 129.28 (2 × quat), 117.63 (4 × CH) and 91.14 (CH_2); *m/z* 272, 270, 268 (3, 15, 23 %), 141 (100), 128 (49), 111 (79), 99 (31) and 75 (68).

Pyrolysis of **1-(1-chloro-4-phenoxymethoxy)-4-chlorobenzene.**

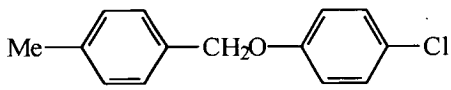
[T_f 750 °C, T_i 140 °C, P 0.01 Torr, t_m 30 min, m_a 0.04 g]

Pyrolysis produced *p*-chlorophenol **235** (66%) δ_H (250 MHz) 7.03 - 7.10 (2H, m, ^3J 8.8) and 6.75 – 6.73 (2H, m, ^3J 8.8); δ_C (63 MHz) 154.38 (quat), 129.38 (quat), 129.35 (2 × CH) and 116.54 (2 × CH). *p*-chlorobenzaldehyde **297** (33%) δ_H (250 MHz) 9.92 (1H, s), 7.77 (2H, d, ^3J 8.2) and 7.45 (2H, d, ^3J 8.2); δ_C (63 MHz) 191.16 (CH), 140.99 (quat), 134.41 (quat), 130.85 (2 × CH) and 129.28 (2 × CH).[yields from ^{1}H NMR]

7.4.6 Attempted Synthesis of 1-(1-methyl-4-chloro-phenoxymethyl)-4-chlorobenzene.

p-Chlorophenol (0.70 g, 5.4 mmol) was dissolved in DMF (25 cm^3). Potassium carbonate (0.57 g, 5.4 mmol) and 4-methylbenzyl bromide (1.00 g, 5.4 mmol) were added and the solution was allowed to stir overnight at room temperature. The mixture was added to water (100 cm^3) and extracted using ether (3 × 100 cm^3). The organics were washed using water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

4-chloro-1-(4-methylbenzyloxy)benzene 284.



(0.80 g, 63%) mp 103 – 105 °C (from ethanol) (Found: C, 72.2; H, 5.15. $C_{14}H_{13}ClO$ requires C, 72.4; H, 5.6%); δ_H (250 MHz) 7.16 – 7.33 (5H, m), 6.74 - 6.79 (3H, m), 5.00 (2H, s) and 2.37 (3H, s); δ_C (63 MHz) 157.24 (quat), 137.78 (quat), 133.36 (quat), 129.33 (quat), 129.17 (4 × CH), 127.46 (2 × CH), 116.01 (2 × CH), 70.07 (CH_2) and 21.07 (CH_3); *m/z* 234, 232 (11 and 18%), 127 (10), 105 (100), 99 (19) and 77 (25).

Attempted Chlorination Reactions.

I/ Using PCl_5

4-Chloro-1-(4-methylbenzyloxy)benzene (0.23 g, 1 mmol) and phosphorus pentachloride (0.21 g, 1.2 mmol) were placed in a Kugelrohr and heated to 145 °C. The temperature was raised slowly to 155 °C so that a gentle reaction was maintained. Once bubbling had ceased, the temperature was raised to 165 °C for 5 min to distil over any remaining PCl_5. The reaction resulted in the recovery of starting material and no desired product.

II/ Using $SOCl_2$

4-Chloro-1-(4-methylbenzyloxy)benzene (0.23 g, 1mmol) was dissolved in dichloromethane (15 cm^3) under dry nitrogen and was heated to reflux. Sulfuryl chloride (0.24 g, 2 mmol) was added dropwise over 1 h period and this was heated to reflux overnight. The solvent was removed under reduced pressure. The reaction resulted in the recovery of starting material and no desired product.

7.4.7 Ethylene Trapping Experiments.

i/ Synthesis of ethyl benzoate.

Benzoic acid (3.00 g, 24 mmol), bromoethane (2.66 g, 24 mmol) and potassium carbonate (3.31 g, 24 mmol) were stirred overnight at room temperature in DMF (30 cm^3). The mixture was added to water (100 cm^3) and extracted using ether (3 × 100 cm^3). The organics were washed using water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. (2.01 g, 79%) δ_H (250 MHz) 7.97 - 8.02 (2H, m), 7.32 - 7.50 (3H, m), 4.31 (2H, q, ^3J 7.1) and 1.33 (3H, t, ^3J 7.1); δ_C (63 MHz) 166.21 (quat), 132.45 (CH), 130.14 (quat), 129.16 (2 × CH), 127.95 (2 × CH), 60.55 (CH_2) and 13.95 (CH_3).

ii/ Pyrolysis Reactions.

In order to trap the ethylene, a different FVP trapping set-up was used. This involved using two U-tubes in series, with bromine in [^{2}H]chloroform distilled in the second U-tube. [The ethylene should react with the bromine *in situ* to give 1,2-dibromoethane] The pyrolyses were carried out as before and when finished, the liquid nitrogen was removed from the first trap (but left around the second trap) and the trap was allowed to warm to room temperature. The liquid nitrogen was then removed from the second trap and the contents of this trap analysed. In each case, the contents of this trap ONLY are reported.

Ethyl benzoate (using Br_2 trap).

[T_f 700 °C, T_i 160 - 200 °C, P 0.012 Torr, t_m 30 min, m_a 0.2 g]

Pyrolysis produced 1,2-dibromoethane[81] δ_H (250 MHz) 3.66 (4H, s); δ_C (63 MHz) 29.99 (2 × CH_2).

2-(*p*-chlorophenoxymethoxy)-pyridine (using Br_2 trap).

[T_f 750 °C, T_i 120 °C, P 0.012 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 1,2-dibromoethane[81] δ_H (250 MHz) 3.68 (4H, s); δ_C (63 MHz) 29.99 (2 × CH_2).

_N_-(_p_-chlorophenoxymethyl)-pyridin-2-one (using Br_2 trap).

[T_f 750 °C, T_i 120 °C, P 0.022 Torr, t_m 20 min, m_a 50 mg]

Pyrolysis produced 1,2-dibromoethane[81] δ_H (250 MHz) 3.67 (4H, s); δ_C (63 MHz) 29.99 (2 × CH_2).

B. ATTEMPTED SYNTHESIS OF THIEPINONES AND AZEPINONES

8.1 Synthesis of 3-substitutedsulfanylpropenals.

i/ Synthesis of Diprop-2-ynyl ether 314.

Propargyl bromide (13.3 g, 0.12 mol) was added to a solution of propargyl alcohol (5.5 g, 0.12 mol) in aqueous potassium hydroxide [potassium hydroxide (7 g) in water (35 cm^3)], at 40 °C. The mixture was heated to reflux with stirring for 2 h. After cooling, the mixture was added to water (100 cm^3) and extracted using ether (3 × 100 cm^3). The organics were washed using water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure and used without further purification. (3.1 g, 28%) δ_H (200 MHz) 4.27 (4H, d, ^3J 1.0) and 2.50 (2H, t, ^3J 1.0);

ii/ Synthesis of propargyl aldehyde 315 (using flash vacuum pyrolysis).

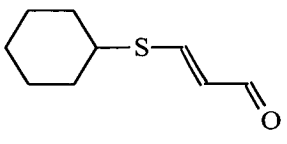
Diprop-2-ynyl ether (2.0 g, 21 mmol) was weighed into a round-bottomed flask and connected *via* a right-angled adapter to an empty furnace tube, held at 750 °C. The inlet flask was cooled in ice and when the system was evacuated to a pressure of 10^{-2} - 10^{-3} Torr, the ether distilled through the furnace tube over a period of 40 - 60 min. The resulting propynal was used without further purification. (0.92 g, 80%) δ_H (200 MHz) 9.16 (1H, s) and 3.51 (1H, s); δ_C (63 MHz) 176.35 (CH), 82.64 (CH) and 74.97 (quat).[97]

iii/ Synthesis of 3-substituted sulfanylpropenals.

Method 1.

Cyclohexanethiol (0.35 g, 3 mmol) and propynal (0.22 g, 4 mmol) were added to chloroform (0.5 cm^3) with stirring at 20 °C. The temperature was increased to 40 °C for 2 h and the solvent was removed under reduced pressure and the resulting oil was purified by Kugelrohr distillation.

3-cyclohexylsulfanylpropenal 317.

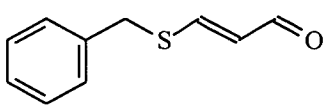


(64%) bp 140 – 142 °C (1 Torr) (Found: M^+, 170.0764. $C_9H_{14}OS$ requires *M*, 170.0762) δ_H (250 MHz) 9.32 (1H, d, ^3J 7.6), 7.57 (1H, d, ^3J 15.2), 6.12 (1H, dd, ^3J 15.2 7.6), 3.09 (1H, m) and 1.17 - 2.04 (10H, m); δ_C (63 MHz) 189.88 (CH), 156.18 (CH), 125.92 (CH), 45.26 (CH), 32.58 (2 × CH_2), 25.48 (2 × CH_2) and 25.15 (CH_2); *m/z* 170 (M^+, 31%), 137 (8), 83 (57), 67 (30) and 55 (100).

Method 2.

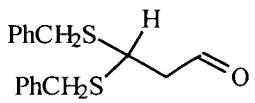
Triethylamine (3 drops) was added to an ice-cooled solution of phenylmethanethiol (0.25 g, 2 mmol) and propynal (0.12 g, 2.2 mmol) in methanol (10 cm^3) with stirring. The solution was allowed to stir for 1 h. and the solvent was removed under reduced pressure. The resulting oil was subjected to dry flash chromatography on silica using hexane : ethyl acetate as eluant.

3-benzylsulfanylpropenal 318.



(23%) bp 107 - 109 °C (1 Torr) [lit.,[159] 107 - 112 °C (1.3 Torr)] (Found: M^+, 178.0452. $C_{10}H_{10}OS$ requires *M*, 178.0452) δ_H (250 MHz) 9.35 (1H, d, ^3J 7.6), 7.54 (1H, d, ^3J 15.2), 7.25 - 7.36 (5H, m), 6.17 (1H, dd, ^3J 15.2 7.6) and 4.06 (2H, s); δ_C (63 MHz) 189.66 (CH), 155.37 (CH), 134.58 (quat), 128.78 (2 × CH), 128.63 (2 × CH), 127.82 (CH), 126.24 (CH), and 36.64 (CH_2); *m/z* 178 (M^+, 11%), 145 (2), 124 (9), 91 (100) and 77 (6).

3,3-bis-benzylsulfanylpropionaldehyde 319.



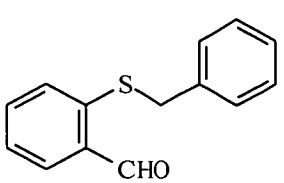
(20%) mp 44 - 45 °C (Found: M^+, 302.0799. $C_{17}H_{18}OS_2$ requires *M*, 302.0799) δ_H (250 MHz) 9.49 (1H, t, ^3J 2.0), 7.24 - 7.36 (10H, m), 4.02 (1H, t, ^3J 7.2), 3.76 - 3.91 (4H, m) and 2.73 (2H, dd, ^3J 7.2, 2.0); δ_C (63 MHz) 198.47 (CH), 137.22 (2 × quat), 128.81 (4 × CH), 128.45 (4 × CH), 127.05 (2 × CH), 48.38 (CH_2), 43.48 (CH) and 34.64 (2 × CH_2); *m/z* 302 (M^+, 1%), 246 (11), 178 (15), 124 (11), 91 (100) and 77 (12).

8.2 Synthesis of *ortho*-substituted benzaldehydes.

Method 1.

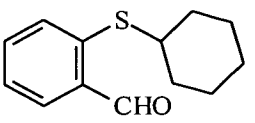
o-Fluorobenzaldehyde (2.5 g, 20 mmol), the appropriate thiol (20 mmol) and potassium carbonate (3 g, 20 mmol) were stirred under reflux in propan-2-ol (35 cm^3) for 20 h. The solution was cooled and poured into water (100 cm^3), extracted with DCM (3 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

2-(benzylthio)benzaldehyde 336a.



(67%) mp 71 – 73 °C [lit.,[106] 72 – 74 °C] δ_H (250 MHz) 10.24 (1H, s), 7.22 - 7.82 (9H, m) and 4.12 (2H, s); δ_C (63 MHz) 191.32 (CH), 140.83 (quat), 135.95 (quat), 134.42 (quat), 133.79 (CH), 131.45 (CH), 129.65 (CH), 128.73 (CH), 128.45 (CH), 127.33 (CH), 125.92 (CH) and 38.67 (CH_2).

2-(cyclohexylthio)benzaldehyde 336b.

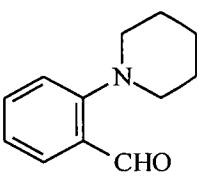


(49%) bp 120 - 124 °C (0.8 Torr) (Found: M^+, 220.0922. $C_{13}H_{16}OS$ requires *M*, 220.0922); δ_H (250 MHz) 10.55 (1H, s), 7.25 - 7.88 (4H, m), 3.11 (1H, m) and 1.23 - 1.99 (10H, m); δ_C (63 MHz) 192.06 (CH), 139.86 (quat), 135.82 (quat), 133.70 (CH), 132.54 (CH), 129.93 (CH), 126.64 (CH), 47.11 (CH), 32.97 (2 × CH_2), 25.84 (2 × CH_2) and 25.48 (CH_2); *m/z* 220 (M^+, 46%), 138 (100), 83 (29) and 77 (12).

Method 2.

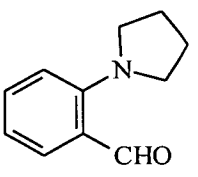
o-Fluorobenzaldehyde (2.0 g, 16 mmol), the appropriate amine (16 mmol) and potassium carbonate (2.21 g, 16 mmol) were stirred under reflux in DMF (35 cm^3) for 5 h. The solution was cooled and poured into water (100 cm^3), extracted with DCM (3 × 50 cm^3), washed with water (2 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting oils were purified by Kugelrohr distillation.

2-piperidin-1-ylbenzaldehyde 336c.



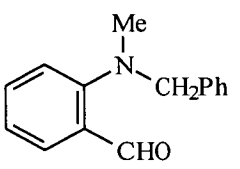
(78%) bp 135 – 137 °C (1 Torr), [lit.,[160] 143 – 144 °C (1 Torr)] δ_H (250 MHz) 10.27 (1H, s), 7.76 – 7.43 (2H, m), 7.00 – 7.25 (2H, m), 2.89 – 3.04 (5H, m) and 1.23 – 1.78 (5H, m); δ_C (63 MHz) 191.53 (CH), 156.81 (quat), 134.64 (quat), 128.96 (CH), 128.38 (quat), 121.76 (CH), 118.78 (CH), 55.43 (2 × CH_2), 26.00 (2 × CH_2) and 23.85 (CH_2).

2-pyrrolidin-1-ylbenzaldehyde 336d.



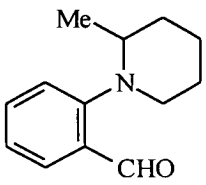
(64%) bp 140 – 150 °C (1 Torr), [lit.,[160] 153 – 154 °C (1 Torr)] δ_H (250 MHz) 10.12 (1H, s), 6.82 – 7.73 (4H, m), 3.22 – 3.48 (4H, m) and 1.98 – 2.15 (4H, m); δ_C (63 MHz) 190.55 (CH), 150.38 (quat), 134.64 (CH), 133.48 (CH), 123.34 (quat), 116.82 (CH), 114.95 (CH), 53.12 (2 × CH) and 26.37 (2 × CH).

2-(*N*-methyl-*N*-benzylamino)-benzaldehyde 336e.



(61%) bp 160 – 162 °C (0.8 Torr) (Found: M^+, 225.1154. $C_{15}H_{15}NO$ requires *M*, 225.1154); δ_H (250 MHz) 10.40 (1H, s), 7.03 - 7.85 (9H, m), 4.34 (2H, s) and 2.81 (3H, s); δ_C (63 MHz) 191.10 (CH), 155.48 (quat), 137.17 (quat), 134.50 (CH), 129.96 (CH), 128.52 (quat), 128.34 (2 × CH), 127.79 (2 × CH), 127.24 (CH), 121.42 (CH), 119.28 (CH), 62.17 (CH_2) and 42.11 (CH_3); *m/z* 225 (M^+, 87%), 148 (31), 134 (55), 120 (47), 119 (15), 105 (47), 104 (41), 91 (100), 78 (44) and 77(64).

2-(2-methylpiperidin-1-yl)-benzaldehyde 336f.



(48%) bp 118 – 120 °C (1 Torr), [lit.,[160] 120 – 122 °C (1 Torr)] δ_H (250 MHz) 10.49 (1H, s), 6.90 – 7.99 (4H, m), 2.77 – 3.20 (4H, m), 1.25 – 1.83 (5H, m) and 0.93 (3H, m);

NOTE

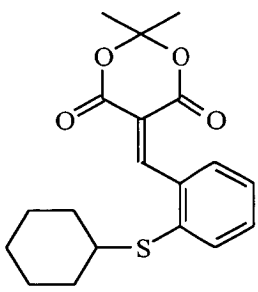
Reactions with methylaniline, dibenzylamine and diisopropylamine under these sets of conditions failed to give any identifiable products other than starting materials.

8.3 Synthesis of Meldrum's Acid derivatives.

Method 1

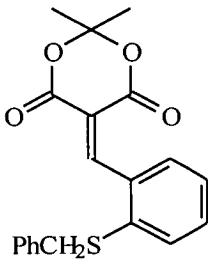
The appropriate aldehyde (5 mmol) was dissolved in pyridine (10 cm^3). Meldrum's acid (0.72 g, 5 mmol) was added and the solution was stirred overnight at room temperature. The mixture was added to ether (30 cm^3) and was washed with a copper (II) sulfate solution (3 × 30 cm^3), then with water (2 × 30 cm^3). The aqueous layers were then combined and washed with ether (2 × 30 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure.

5-(2-cyclohexylsulfanylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 337a.



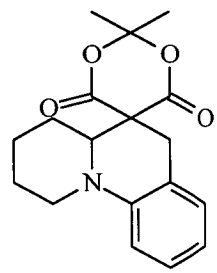
(45%) bp 140 - 144 °C (1 Torr) (Found: M^+, 346.1232. $C_{19}H_{22}O_4S$ requires *M*, 346.1239); δ_H (250 MHz) 8.89 (1H, s), 7.18 - 7.89 (4H, m), 3.10 (1H, m) and 1.22 - 2.16 (16H, m) [6H from Meldrum's acid superimposed]; δ_C (63 MHz) 162.48 (quat), 159.47 (quat), 156.81 (CH), 138.37 (quat), 134.50 (quat), 131.97 (CH), 131.85 (CH), 131.06 (CH), 126.21 (CH), 115.94 (quat), 104.56 (quat), 48.19 (CH), 33.06 (2 × CH_2), 27.62 (2 × CH_3), 25.80 (2 × CH_2) and 25.42 (CH_2); *m/z* 346 (M^+, 4%), 288 (3), 220 (61), 138 (100) and 83 (78).

5-(2-benzylsulfanylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 337b.



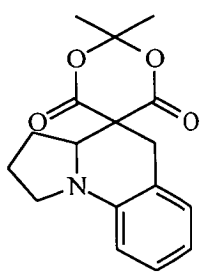
(56%) mp 85 – 86 °C (from hexane and ethyl acetate) (Found: C, 67.75; H, 5.5; $C_{20}H_{18}O_4S$ requires C, 67.8; H, 5.05%) (Found: M^+, 354.0929. $C_{20}H_{18}O_4S$ requires *M*, 354.0926); δ_H (250 MHz) 8.70 (1H, s), 7.18 - 7.68 (9H, m), 4.06 (2H, s) and 1.79 (6H, s); δ_C (63 MHz) 162.25 (quat), 159.34 (quat), 156.28 (CH), 138.29 (quat), 136.48 (quat), 134.08 (quat), 133.84 (CH), 131.95 (CH), 131.45 (CH), 130.85 (CH), 128.76 (CH), 128.51 (CH), 127.29 (CH), 126.52 (CH), 116.25 (quat), 104.58 (quat), 40.32 (CH_2) and 27.65 (2 × CH_3); *m/z* 354 (M^+, 0.4%), 296 (7), 278 (1), 228 (68), 137 (87), 109 (56) and 91 (100).

2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-5,5-*spiro*[5,5-(2,2-dimethyl-1,3-di oxane-4,6-dione)] 339.



(54%) mp 149 – 150 °C (from ethanol) (Found: C, 68.4; H, 6.45; N, 4.25. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.65; N, 4.45%); δ_H (250 MHz) 6.97 – 7.14 (3H, m), 6.73 (1H, m), 4.12 (1H, m), 3.53 (1H, d, ^2J 16.4), 3.43 (1H, m), 3.13 (1H, d, ^2J 16.4), 2.73 - 2.79 (1H, m) and 1.34 – 1.86 (12H, m) [6H from Meldrum's acid superimposed]; δ_C (63 MHz) 169.21 (quat), 164.74 (quat), 144.67 (quat), 128.55 (CH), 127.44 (CH), 119.20 (quat), 118.09 (CH), 113.21 (CH), 104.89 (quat), 61.53 (CH), 51.99 (quat), 48.48 (CH_2), 34.18 (CH_2), 30.16 (CH_3), 27.94 (CH_3 and CH_2) [2 peaks superimposed], 24.37 (CH_2) and 23.75 (CH_2); *m/z* 315 (M^+, 21%), 257 (1), 213 (57), 185 (19), 157 (49) 77 (21) and 43 (100).

1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*]quinoline-4,4-*spiro*[5,5-(2,2-dimethyl-1,3-di oxane-4,6-dione] 346.



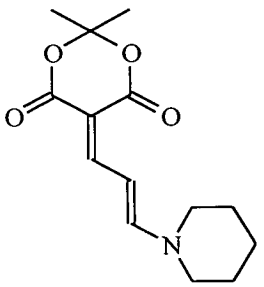
(40%) mp 183 – 184 °C (from ethanol) (Found: C, 67.7; H, 6.35; N, 4.5; $C_{17}H_{19}NO_4$ requires C, 67.75; H, 6.3; N, 4.65%); δ_H (250 MHz) 7.02 – 7.20 (2H, m), 6.59 – 6.69 (2H, m), 3.96 (1H, m), 3.64 (1H, m), 3.55 (1H, d, ^2J 16.2), 3.30 (1H, m), 3.13 (1H, d, ^2J 16.2) and 1.56 – 2.25 (10H, m); δ_C (63 MHz) 169.98 (quat), 163.97 (quat), 142.99 (quat), 128.11 (CH), 127.67 (CH), 116.81 (quat), 115.95 (CH), 111.37 (CH), 104.59 (quat), 64.54 (CH), 47.74 (CH_2), 47.12 (quat), 36.36 (CH_2), 29.89 (CH_3), 28.33 (CH_2), 28.00 (CH_3) and 23.03 (CH_2); *m/z* 301 (M^+, 71%), 243 (3), 199 (86), 198 (100), 171 (39), 146 (5), 91 (18) and 77 (18).

Method 2

A suspension of 2,2-dimethyl-1,3-dioxan-4,6-dione (2 mmol) and appropriate aldehyde or sulfanyl-propenyl (2 mmol) in toluene (3 cm^3) was treated with acetic acid (4 drops) and piperidine (4 drops), the mixture was then stirred at room temperature for 1 h and the solvent removed under reduced pressure. The resulting mixture was subjected to dry flash chromatography on silica using hexane : ethyl acetate.

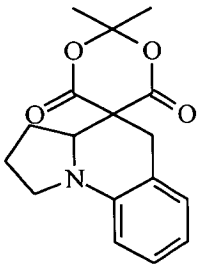
-When 3-cyclohexylsulfanylpropenal was used as a precursor, the only isolated product was 5-[-3-(piperidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxan-4,6-dione. This is due to the reaction of the piperidine catalyst with the sulfanylpropenal and subsequent reaction with Meldrum's acid.

5-[-3-(Piperidin-1-yl)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 323.



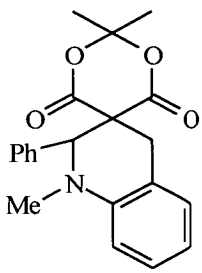
[3-cyclohexylsulfanylpropenal] (7%) mp 166 – 167 °C [lit.,[99] 167 – 169 °C] δ_H (250 MHz) 7.95 (1H, d, ^3J 13.2), 7.25 (1H, d, ^3J 12.1), 6.98 (1H, dd, ^3J 13.2 and 12.1), 3.56 – 3.58 (4H, m), 1.73 (6H, s) and 1.67 (6H, s); δ_C (63 MHz) 165.43 (quat), 163.54 (quat), 161.24 (CH), 158.66 (CH), 103.02 (quat), 101.75 (CH), 93.71 (quat), 56.47 (CH_2), 47.60 (CH_2), 26.89 (2 × CH_3), 26.58 (CH_2), 25.21 (CH_2) and 23.53 (CH_2).

1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*]quinoline-4,4-*spiro*[5,5-(2,2-dimethyl-1,3-dioxane-4,6-dione] 346.



[2-pyrrolidin-1-ylbenzaldehyde] (82%) (as above) mp 183 - 184 °C (from ethanol) [method of choice for this compound due to higher yield.]

1-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-3,3-*spiro*[5,5-(2,2-dimethyl-1,3-di oxane-4,6-dione] 345.



[2-(*N*-methyl-*N*-benzylamino)benzaldehyde] (45%) mp 138 – 140 °C (from ethanol) (Found: C, 71.75; H, 5.95; N, 3.9. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%); δ_H (250 MHz) 7.19 – 7.34 (6H, m), 6.72 – 7.02 (3H, m), 4.87 (1H, s), 3.63 (1H, d, ^3J 16.2), 3.16 (1H, d, ^3J 16.2), 2.82 (3H, s), 1.62 (3H, s) and 1.01 (3H, s); δ_C (63 MHz) 168.46 (quat), 163.74 (quat), 145.76 (quat), 136.74 (quat), 128.78 (3 × CH), 128.50 (2 × CH), 127.92 (CH), 127.78 (CH), 118.36 (quat), 117.28 (CH), 112.27 (CH), 105.20 (quat), 67.24 (CH), 53.54 (quat), 37.79 (CH_3), 35.77 (CH_2), 29.51 (CH_3) and 27.76 (CH_3); *m/z* 351 (M^+, 50%), 249 (89), 248 (100), 234 (15), 144 (46), 91 (35) and 77 (29).

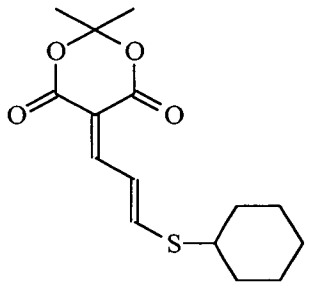
NOTE.

Reaction with 2-(2-methylpiperidin-1-yl)-benzaldehyde resulted in the formation of no identifiable products by ^{1}H NMR spectroscopy.

Method 3

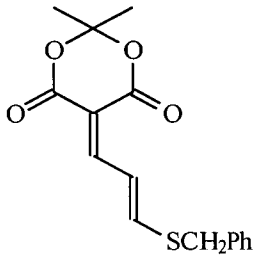
A solution of titanium tetrachloride (4 mmol) in carbon tetrachloride (1 cm^3) was added dropwise to ice-cold tetrahydrofuran (8 cm^3). This was followed by slow addition of a solution of 2,2-dimethyl-1,3-dioxan-4,6-dione (2 mmol) and the 3-substituted sulfanylpropenal (2 mmol) in tetrahydrofuran (2 cm^3), and then by a solution of pyridine (0.8 cm^3) in tetrahydrofuran (1 cm^3). The stirring was continued for 1 h at 0 °C, and at room temperature overnight, after which water (10 cm^3) and ether (20 cm^3) were added. The organic layer was separated, washed with brine (2 × 20 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was subjected to dry flash chromatography on silica using hexane : ethyl acetate as eluant.

5-[-3-(cyclohexylthio)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 322.



(36%) mp 167 – 169 °C (from acetonitrile) (Found: C, 60.0; H, 6.7. $C_{15}H_{20}O_4S.0.2H_2O$ requires C, 60.05; H, 6.75%) (Found: M^+, 296.1085. $C_{15}H_{20}O_4S$ requires *M*, 296.1087); δ_H (250 MHz) 7.71 – 7.95 (3H, m), 3.27 (1H, m), 1.29 – 2.15 (10H, m) and 1.71 (6H, s); δ_C (63 MHz) 163.51 (quat), 161.13 (quat), 160.11 (CH), 156.02 (CH), 122.37 (CH), 105.10 (quat), 104.26 (quat), 46.41 (CH), 32.76 (2 × CH_2), 27.40 (2 × CH_3), 25.47 (2 × CH_2) and 25.16 (CH_2); *m/z* 296 (M^+, 8%), 269 (3), 238 (3), 181 (30), 123 (100), 115 (58) and 83 (45).

5-[-3-(benzylthio)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 324.



(32%) mp 101 - 102 °C (from ethanol) (Found: C, 62.75; H, 5.0. $C_{16}H_{16}O_4S$ requires C, 63.15; H, 5.25%) (Found: M^+, 304.0775. $C_{16}H_{16}O_4S$ requires *M*, 304.0775) δ_H (250 MHz) 7.56 - 7.88 (3H, m), 7.35 - 7.38 (5H, m), 4.18 (2H, s) and 1.70 (6H, s); δ_C (63 MHz) 163.29 (quat), 160.95 (quat), 158.40 (CH), 155.54 (CH), 134.50 (quat), 128.93 (2 × CH), 128.88 (2 × CH), 127.99 (CH), 122.22 (CH), 106.03 (quat), 104.34 (quat), 37.35 (CH_2) and 27.40 (2 × CH_3); *m/z* 304 (M^+, 14%), 246 (34), 228 (5), 181 (91), 123 (81) and 84 (100).

8.4 Pyrolysis of sulfur-containing Meldrum's acid derivatives.

The appropriate derivative was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent to enable removal from the trap. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets.

5-(2-benzylsulfanylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione. [T_f 525 °C, T_i 150 °C, P 0.004 Torr, t_m 30 min, m_a 0.03 g]

Examination of the pyrolysate by ^{1}H NMR spectroscopy showed the presence of bibenzyl[161] (46%) δ_H (200 MHz) 7.85 (10H, m) and 2.96 (4H, s) and no other identifiable products. Pyrolysis at lower temperatures gave only recovered starting material.

5-(2-cyclohexylsulfanylbenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione.[T_f 600 °C, T_i 150 °C, P 0.004 Torr, t_m 30 min, m_a 0.3 g]

Examination of the pyrolysate by ^{1}H NMR spectroscopy showed the presence of no identifiable products. Pyrolysis at higher and lower temperatures gave the same result.

5-[-3-(benzylthio)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione [T_f 600 °C, T_i 150 °C, P 0.004 Torr, t_m 30 min, m_a 0.03 g]

Examination of the pyrolysate by ^{1}H NMR spectroscopy showed the presence of bibenzyl[161] (32%) δ_H (200 MHz) 7.16 - 7.87 (10H, m) and 2.92 (4H, s); δ_C (63 MHz) 129.30 (2 × quat), 128.32 (4 × CH), 128.21 (4 × CH), 125.78 (2 × CH) and 37.82 (CH_2) and no other identifiable products.

5-[-3-(cyclohexylthio)propenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione

[T_f 600 °C, T_i 150 °C, P 0.004 Torr, t_m 30 min, m_a 0.3 g]

Examination of the pyrolysate by ^{1}H NMR spectroscopy showed the presence of no identifiable products. Pyrolysis at higher and lower temperatures gave the same result.

8.5 Attempted cyclisation of 5-[(2-benzylthiophenyl)methylene]–2,2-dimethyl-1,3-dioxane-4,6-dione.

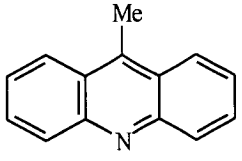
The 5-[(2-benzylthiophenyl)methylene]–2,2-dimethyl-1,3-dioxane-4,6-dione (1.00 g, 2.8 mmol) was dissolved in 1-butanol (20 cm^3) and refluxed for 5 h. The mixture was cooled and the solvent removed under reduced pressure. The ^{1}H NMR spectrum of the resulting oil showed only the presence of starting material and no cyclised product.

C. PYROLYSIS OF SEVEN-MEMBERED RINGS.

9.1 Pyrolysis of 5*H*-dibenzo[*b*,*f*]azepine.

[T_f 950 °C, T_i 180 – 200 °C, P 0.0092 Torr, t_m 30 min, m_a 350 mg]

Pyrolysis produced 9-methylacridine **355** after dry flash chromatography on silica using hexane : ethyl acetate as eluant.

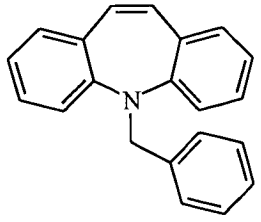


(210 mg, 60%) δ_H (250 MHz) 8.14 – 8.21 (4H, m), 7.45 – 7.75 (4H, m) and 3.02 (3H, s); δ_C (63 MHz) 148.14 (2 × quat), 142.14 (quat), 129.93 (2 × CH), 129.58 (2 × CH), 125.46 (2 × quat), 125.19 (2 × CH), 124.34 (2 × CH) and 13.41 (CH_3).[162]

9.2 Alkylation of 5*H*-dibenzo[*b*,*f*]azepine.

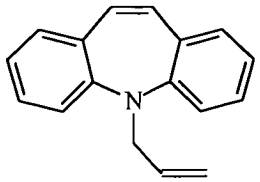
Powdered potassium hydroxide (1.5 g) was added to DMSO (10 cm^3) and allowed to stir for 10 min. 5*H*-Dibenzo[*b*,*f*]azepine (1.0 g, 5.2 mmol) was added and the solution was stirred for 90 min. The appropriate alkyl halide (10.4 mmol) was added and the solution was stirred for 90 min. The solution was added to water (100 cm^3) and extracted with DCM (3 × 100 cm^3). The organic layer was washed with water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was subjected to dry flash chromatography on silica using hexane as eluant.

5-Benzyl-5*H*-dibenzo[*b*,*f*]azepine 360.



(35%) mp 81 - 83 °C (from hexane) [lit.,[163] 80 °C] (Found: C, 89.2; H, 6.2; N, 5.15. $C_{21}H_{17}N$ requires C, 89.05; H, 6.0; N, 4.95%); δ_H (250 MHz) 7.03 - 7.63 (11H, m), 6.72 - 6.77 (2H, m), 6.57 (2H, s) and 4.81 (2H, s); δ_C (63 MHz) 138.14 (2 × quat), 131.98 (3 × CH), 130.33 (2 × CH), 129.33 (2 × CH), 128.53 (quat), 128.28 (2 × CH), 127.67 (2 × CH), 127.51 (2 × CH), 123.00 (2 × quat), 119.23 (2 × CH) and 71.99 (CH_2); *m/z* 283 (M^+, 6%), 217 (100), 194 (14), 149 (2) and 91 (77).

5-Allyl-5*H*-dibenzo[*b*,*f*]azepine.365.



(46%) mp 55 – 56 °C [lit.,[164] 55 - 57 °C] (Found: M^+, 233.1200. $C_{17}H_{15}N$ requires *M*, 233.1205) δ_H (250 MHz) 7.22 – 7.29 (2H, m), 6.96 – 7.10 (6H, m), 6.77 (2H, m), 5.80 (1H, m), 5.32 (1H, m), 5.12 (1H, m) and 4.40 – 4.43 (2H, m); δ_C (63 MHz) 150.54 (2 × quat), 135.07 (CH), 133.58 (2 × quat), 132.06 (2 × CH), 128.97 (2 × CH), 128.52 (2 × CH), 123.21 (2 × CH), 120.40 (2 × CH), 117.47 (CH_2) and 53.39 (CH_2); *m/z* 233 (M^+, 19%), 192 (100), 165 (15), 139 (7), 89 (6) and 77 (6).

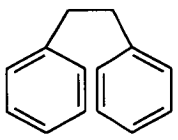
9.3 Pyrolysis of alkylated 5*H*-dibenzo[*b*,*f*]azepine derivatives.

The appropriate derivative was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent to enable removal from the trap. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets..

5-Benzyl-5*H*-dibenzo[*b*,*f*]azepine

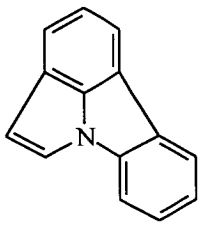
[T_f 750 °C, T_i 150 °C, *P* 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced bibenzyl[161] **331** (55% combined yield with **361** as could not be separated by chromatography)

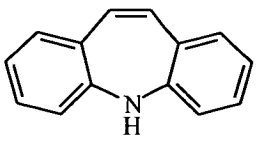


δ_H (200 MHz) 7.16 - 7.87 (10H, m) and 2.92 (4H, s); δ_C (63 MHz) 129.30 (2 × quat), 128.32 (4 × CH), 128.21 (4 × CH), 125.78 (2 × CH) and 37.82 (2 × CH_2);

pyrrolo[3,2,1-*jk*]carbazole **361** mp 88 - 89 °C [lit.,[118] 89 - 90 °C]



δ_H (360 MHz) 8.08 (1H, ddd, ^3J 7.8, ^4J 1.2, ^5J 0.7), 7.90 (1H, dd, ^3J 7.4, ^4J 0.5), 7.79 (1H, dd, ^3J 7.4, ^4J 0.5), 7.73 (1H, d, ^3J 3.1), 7.68 (1H, ddd, ^3J 8.0, ^4J 1.0, ^5J 0.7), 7.51 (1H, t, ^3J 7.4), 7.47 (1H, td, ^3J 8.0, ^4J 1.2), 7.32 (1H, td, ^3J 7.8, ^4J 1.0) and 6.86 (1H, d, ^3J 3.1); δ_C (90 MHz) 141.32 (quat), 139.85 (quat), 131.41 (quat), 127.01 (CH), 123.91 (CH), 123.62 (CH), 122.93 (CH), 122.63 (CH), 122.14 (quat), 121.54 (CH), 119.43 (quat), 117.84 (CH), 111.91 (CH) and 109.86 (CH); 9-methylacridine **355** (as above) (2%) and 5*H*-dibenzo[*b*,*f*]azepine **348** (20%)



δ_H (250 MHz) 7.03 - 7.10 (2H, m), 6.82 - 6.93 (4H, m), 6.51 - 6.55 (2H, m) and 6.35 (2H, s); δ_C (63 MHz) 148.23 (2 × quat), 131.99 (2 × CH), 130.37 (2 × CH), 129.60 (2 × quat), 129.32 (2 × CH), 122.89 (2 × CH) and 119.18 (2 × CH).

5-Allyl-5*H*-dibenzo[*b*,*f*]azepine. [yield from ^{1}H NMR]

[T_f 750 °C, T_i 150 °C, P 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole (56%), iminostilbene (43%) and 9-methylacridine (1%)

[T_f 800 °C, T_i 150 °C, P 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole (60%), iminostilbene (38%) and 9-methylacridine (2%)

[T_f 850 °C, T_i 150 °C, P 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole (80%), iminostilbene (16%) and 9-methylacridine (4%)

[T_f 900 °C, T_i 150 °C, P 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole (88%), iminostilbene (8%) and 9-methylacridine (3%)

[T_f 950 °C, T_i 150 °C, P 0.04 Torr, t_m 20 min, m_a 0.05 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole (96%), iminostilbene (1%) and 9-methylacridine (3%)

5-Allyl-5*H*-dibenzo[*b*,*f*]azepine. (preparative scale)

[T_f 950 °C, T_i 150 °C, P 0.04 Torr, t_m 60 min, m_a 1.1 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole (0.57 g, 63%) after dry flash chromatography on silica using hexane as eluant.(as above)

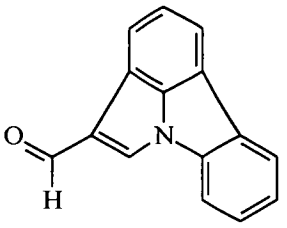
9.4 Some Reactions of pyrrolo[3,2,1-*jk*]carbazole.

9.4.1 Vilsmeier Reaction.

Phosphoryl chloride (3 cm^3) was dissolved in DMF (15 cm^3) under an atmosphere of dry nitrogen. A solution of pyrrolo[3,2,1-*jk*]carbazole (0.29 g, 1.5 mmol) in DMF (5 cm^3) was added dropwise. The mixture was allowed to stir overnight at room temperature. The reaction mixture was neutralised with 2M sodium hydroxide, extracted with ether (3 × 100 cm^3), dried ($MgSO_4$) and the solvent

removed under reduced pressure. The residue was subjected to dry flash chromatography on silica using hexane : ethyl acetate (1:1) as eluant.

Pyrrolo[3,2,1-*jk*]carbazole-4-carboxaldehyde 370.

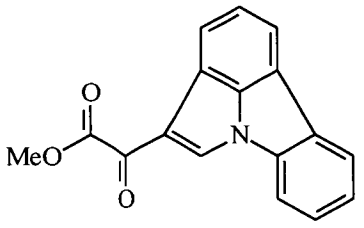


(80 mg, 15%) mp 137 – 139 °C (from hexane and toluene) (Found: C, 80.85; H, 4.1; N, 6.2. $C_{15}H_9NO$ requires C, 80.55; H, 4.25; N, 6.25%) (Found: M^+, 219.0685. $C_{15}H_9NO$ requires *M*, 219.0684); δ_H (250 MHz) 10.02 (1H, s), 8.08 (1H, s), 8.06 (1H, d, ^3J 7.4), 7.92 (1H, ddd, ^3J 7.4, ^4J 1.4, ^5J 0.7), 7.76 (1H, d, ^3J 7.4), 7.58 (1H, ddd, ^3J 7.4, ^4J 1.2, ^5J 0.7), 7.51 (1H, t, ^3J 7.4), 7.42 (1H, td, ^3J 7.4, ^4J 1.4) and 7.34 (1H, td, ^3J 7.4, ^4J 1.2); δ_C (63 MHz) 185.11 (CH), 141.12 (quat), 138.20 (quat), 131.70 (quat), 130.99 (CH), 126.96 (CH), 126.42 (quat), 125.68 (CH), 124.33 (CH), 123.16 (CH), 122.28 (CH), 119.08 (quat), 118.73 (CH), 117.82 (quat) and 112.38 (CH); *m/z* 219 (M^+, 94%), 218 (100), 190 (45), 163 (16), 140 (6), 96 (20) and 82 (12).

9.4.2 Reaction with oxalyl chloride.

Pyrrolo[3,2,1-*jk*]carbazole (0.09 g, 0.5 mmol) was dissolved in an excess of oxalyl chloide (1.5 cm^3) and stirred at room temperature for 1 h. The excess oxalyl chloride was removed under reduced pressure and methanol was added dropwise. The solvent was then removed under reduced pressure and the resulting mixture was subjected to dry flash chromatography on silica using hexane : ethyl acetate as eluant.

Oxo-pyrrolo[3,2,1-*jk*]carbazol-4-yl-acetic acid methyl ester 369.



(63 mg, 48%) mp 152 - 153 °C (from ethanol) (Found: C, 74.75; H, 4.15; N, 5.05. $C_{17}H_{11}NO_3$ requires C, 73.65; H, 4.0; N, 5.05%) (Found: M^+, 277.0739. $C_{17}H_{11}NO_3$ requires *M*, 277.0739) δ_H (250 MHz) 8.89 (1H, s), 8.21 (1H, d, ^3J 7.6), 8.03 (1H, ddd, ^3J 7.5, ^4J 1.3, ^5J 0.6), 7.86 (1H, d, ^3J 7.6), 7.74 (1H, ddd, ^3J 7.5, ^4J 1.3, ^5J 0.6), 7.61 (1H, t, ^3J 7.6), 7.51 (1H, td, ^3J 7.5, ^4J 1.3), 7.44 (1H, td, ^3J 7.5, ^4J 1.1) and 4.08 (3H, s); δ_C (63 MHz) 177.85 (quat), 162.59 (quat), 140.82 (quat), 138.34 (quat), 132.28 (quat), 131.79 (CH), 127.15 (CH), 126.18 (CH), 124.85 (CH), 123.65 (CH), 123.37

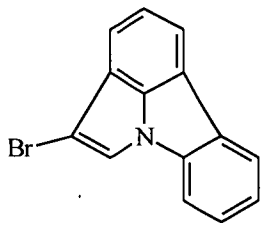
(CH), 121.54 (quat), 119.69 (quat), 119.31 (quat), 118.86 (CH), 112.86 (CH) and 52.89 (CH_3); *m/z* 277 (M^+, 25%), 218 (100), 190 (41), 163 (12) and 109 (11).

9.4.3 Halogenation Reactions.

9.4.3.1 Bromination Reaction.

Pyrrolo[3,2,1-*jk*]carbazole (1 mmol) was dissolved in DMF (10 cm^3) under dry nitrogen. A solution of bromine (0.15 g) in DMF (5 cm^3) was added and the solution stirred for 15 min. The reaction mixture was then poured into ice and water (50 cm^3) containing ammonia (0.5%) and sodium metabisulfite (0.1%). The emulsion was extracted using hexane and ethyl acetate (1:1, v/v) and the organic layer was then washed with water (2 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

4-Bromopyrrolo[3,2,1-*jk*]carbazole 375.

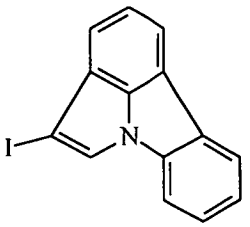


(103 mg, 21%) mp 70 – 72 °C (decomposition) (Found: M^+, 269.9909. $C_{14}H_8{}^{81}BrN$ requires *M*, 269.9874); δ_H (250 MHz) 8.07 (1H, ddd, ^3J 7.6, ^4J 1.1, ^5J 0.6), 7.91 (1H, d, ^3J 7.4), 7.76 (1H, s), 7.72 (1H, d, ^3J 7.4), 7.63 (1H, dd, ^3J 7.6, ^4J 1.0), 7.56 (1H, t, ^3J 7.4), 7.48 (1H, td, ^3J 7.6, ^4J 1.1) and 7.35 (1H, td, ^3J 7.6, ^4J 1.0); δ_C (90 MHz) 171.51 (quat), 139.96 (quat), 130.23 (quat), 127.41 (CH), 124.44 (CH), 123.68 (CH), 123.06 (CH), 122.09 (CH), 122.02 (quat), 120.11 (quat), 119.99 (CH), 118.82 (CH), 111.90 (CH), and 98.10 (quat); *m/z* 271, 269 (M^+, 30 and 32%), 190 (20), 169 (34), 121 (100) and 95 (37).

9.4.3.2 Iodination Reaction.

Solid iodine (1.0 g, 4 mmol) was added to a solution of the pyrrolo[3,2,1-*jk*]carbazole (0.38 g, 2 mmol) dissolved in DMF (10 cm^3), in the presence of potassium hydroxide pellets (0.42 g, 7.5 mmol) with stirring, under dry nitrogen. The reaction mixture was then poured into ice and water (50 cm^3) containing ammonia (0.5%) and sodium metabisulphite (0.1%). The emulsion was extracted using hexane and ethyl acetate (1:1, v/v) and the organic layer was then washed with water (2 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

4-iodopyrrolo[3,2,1-*jk*]carbazole 376.

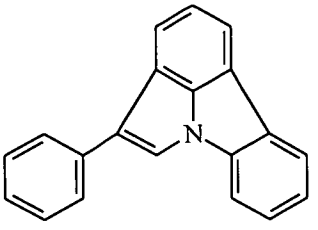


(217 mg, 34%) mp 86 – 88 °C (decomposition) (Found: M^+, 316.9701. $C_{14}H_8IN$ requires *M*, 316.9701); δ_H (250 MHz) 8.07 (1H, ddd, ^3J 7.6, ^4J 1.3, ^5J 0.8), 7.91 (1H, m), 7.81 (1H, s), 7.65 (1H, ddd, ^3J 7.6, ^4J 1.0, ^5J 0.8), 7.57 – 7.59 (2H, m), 7.50 (1H, td, ^3J 7.6, ^4J 1.3) and 7.36 (1H, td, ^3J 7.6, ^4J 1.0); δ_C (90 MHz) 140.67 (quat), 139.66 (quat), 130.41 (quat), 127.35 (CH), 126.48 (CH), 125.06 (quat), 124.50 (CH), 123.72 (CH), 123.19 (CH), 121.17 (CH), 120.01 (quat), 118.76 (CH), 112.07 (CH) and 63.26 (quat); *m/z* 317 (M^+, 37%), 280 (47), 190 (38), 173 (94), 165 (38), 145 (43), 107 (49) and 91 (100).

9.4.4 Suzuki Reaction of the 4-iodopyrrolo[3,2,1-*jk*]carbazole.

Under an atmosphere of nitrogen in the dark, the 4-iodopyrrolo[3,2,1-*jk*]carbazole (0.38 g, 1 mmol) and tetrakistriphenylphosphine palladium (0.03 g, 0.03 mmol) were added to DME (5 cm^3) and stirred at room temperature for 1 h. Sodium carbonate (0.07 g, 0.8 mmol), phenylboronic acid (0.10 g, 0.8 mmol) and water (5 cm^3) were then added and the reaction heated to reflux for 6 h and stirred for a further 72 h at room temperature. The solvents were removed under reduced pressure and water (50 cm^3) was added. This was extracted with DCM (3 × 50 cm^3), the organics were dried ($MgSO_4$) and passed through an alumina pad. The resulting residue was subjected to dry flash chromatography on silica using hexane : ethyl acetate as eluant.

4-Phenylpyrrolo[3,2,1-*jk*]carbazole 377.



(22%) mp 113 - 114 °C (from hexane) (Found: M^+, 267.0990. $C_{20}H_{13}N$ requires *M*, 267.1048); δ_H (360 MHz) 7.37 – 8.13 (13H, m); δ_C (90 MHz) 141.85 (quat), 139.65 (quat), 135.81 (quat), 131.15 (quat), 129.43 (2 × CH), 127.19 (CH), 126.99 (2 × CH), 124.27 (CH), 124.06 (quat), 123.56 (CH), 122.91 (quat), 122.76 (CH), 121.69 (CH), 119.41 (quat), 118.97 (CH), 118.27 (CH), 117.82 (CH) and 111.91 (CH); *m/z* 267 (M^+, 29%), 241 (6), 191 (100), 163 (57), 139 (25), 96 (89) and 81 (47).

NOTE: The following two reactions were attempted but failed to give the desired compound.

1/ 2,2-Dimethyl-5-methoxymethylene-1,3-dioxane-4,6-dione (MMMA).

Pyrrolo[3,2,1-*jk*]carbazole (0.5 mmol) was dissolved in acetonitrile (10cm^3) and MMMA (0.5 mmol) was added. The solution was allowed to stir overnight. ^{1}H NMR spectroscopy showed the presence of starting materials even after several hours at elevated temperatures.

2/ Trifluoroacetic acid (TFA).

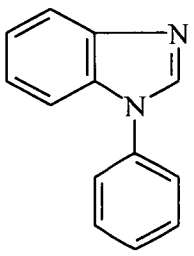
Pyrrolo[3,2,1-*jk*]carbazole (20 mg) was added to TFA and there was immediate decomposition of this compound which could not be overcome.

9.5 Extension to 5*H*-dibenzo[*b,f*]azepine analogues.

1/ Attempted synthesis of 5*H*-dibenzo[*b,e*][1,4]diazepine.

Butyllithium (0.1 mol) was added dropwise to a stirred solution of 2-aminodiphenylamine (0.01 mol) in ether (20cm^3) at room temperature, under dry nitrogen. The reaction mixture is stirred for 48 h at room temperature and DMF (0.1 mol) in dry ether (10 cm^3) is added slowly. The mixture is stirred for 1 h and then decomposed with water (25 cm^3). The aqueous layer is extracted with ether (3 × 25 cm^3) and the ether layer washed with water. The ether layer is extracted with 1M HCl (3 × 25 cm^3) and the aqueous extract made alkaline with NaOH. This is then extracted with ether (3 × 25 cm^3). The material obtained is recrystallised from ether.

***N*-phenylbenzimidazole 382.**



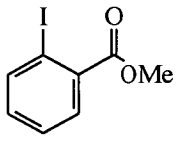
(30%) mp 93 - 94 °C (from ether) [lit.,[81] 98 °C] δ_H (250 MHz) 8.13 (1H, s), 7.88 (1H, m), 7.31 – 7.62 (7H, m); δ_C (90 MHz) 140.67 (quat), 139.66 (quat), 130.41 (quat), 127.35 (CH), 126.48 (CH), 125.06 (quat), 124.50 (CH), 123.72 (CH), 123.19 (CH),

D. Synthesis and Pyrolysis of *o*-substituted aromatic esters and carboxylic acids.

10.1 Synthesis of Methyl 2-iodobenzoate.

2-Iodobenzoic acid (10 g, 0.04 mol), potassium carbonate (6.62 g, 0.048 mol) and methyl iodide (6.25 g, 0.044 mol) were added to DMF (35 cm^3) and stirred overnight at room temperature. The mixture was added to water (100 cm^3) and this was extracted with ether (3 × 100 cm^3). The organic layer was washed with water (2 × 100 cm^3) and the combined organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure.

Methyl 2-iodobenzoate 403.



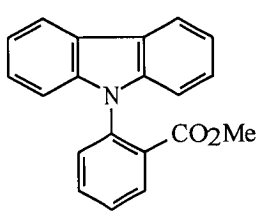
(8.77 g, 84%) bp 102 - 103 °C (1 Torr) [lit.,[165] 103.5 °C (1Torr)] δ_H (250 MHz) 7.90 (1H, ddd, ^3J 7.5, ^4J 1.2, ^5J 0.4), 7.71 (1H, ddd, ^3J 7.4, ^4J 1.8, ^5J 0.4), 7.31 (1H, td, ^3J 7.4, ^4J 1.2), 7.05 (1H, td, ^3J 7.5, ^4J 1.8) and 3.85 (3H, s); δ_C (63 MHz) 166.50 (quat), 140.90 (CH), 134.64 (quat), 132.32 (CH), 130.57 (CH), 127.56 (CH), 93.75 (quat) and 52.15 (CH_3).

10.2 *N*-Arylation of heterocycles by *o*-halogenobenzoic esters.

Method 1.

A mixture of heterocycle (20.7 mmol), methyl 2-iodobenzoate (30 mmol), copper-bronze powder (0.90 g), potassium carbonate (30 mmol) and nitrobenzene (2 cm^3) was heated to 170 – 180 °C for 40 h. The reaction mixture was added to a chloroform: water mixture (200 cm^3; 1:1). The layers were separated and the aqueous layer was extracted with chloroform (3 × 100 cm^3). The combined organics were dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting oil was subjected to dry flash chromatography on silica using hexane : ethyl acetate as eluant. The following were made by this method.

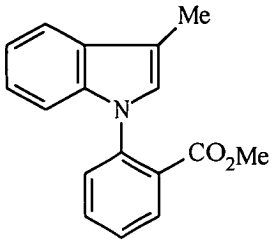
Methyl 2-carbazol-9-ylbenzoate 401.



(2.89 g, 46%) mp 149 – 150 °C [lit.,[129] 150 – 151 °C]; δ_H (250 MHz) 8.11 – 8.18 (3H, m), 7.75 (1H, m), 7.24 – 7.63 (6H, m), 7.15 (2H, dt ^3J 7.1, ^4J 0.9) and 3.21 (3H, s); δ_C (63 MHz) 166.30 (quat), 141.46 (2 × quat), 136.80 (quat), 133.23 (CH), 131.86 (CH), 129.97 (CH), 129.92 (2 × quat), 128.15 (CH), 125.81 (2 × CH),

123.14 (quat), 120.14 (2 × CH), 119.66 (2 × CH), 109.15 (2 × CH) and 51.96 (CH_3).

Methyl 2-(3-methyl 2-indol-1-ylbenzoate 408.



(0.7 g, 35%) mp 100 – 101 °C; (Found: C, 76.3; H, 5.75; N, 5.3. $C_{17}H_{15}NO_2.0.1H_2O$ requires C, 76.45, H, 5.65, N, 5.3%); (Found: M^+, 265.1103. $C_{17}H_{15}NO_2$ requires *M*, 265.1103); δ_H (250 MHz) 6.98 – 7.96 (9H, m), 3.46 (3H, s) and 2.38 (3H, s); δ_C (63 MHz) 166.95 (quat), 148.55 (quat), 138.73 (quat), 137.21 (quat), 132.57 (CH), 131.02 (CH), 129.08 (quat), 128.53 (quat), 128.09 (CH), 126.96 (CH), 126.18 (CH), 122.13 (CH), 119.39 (CH), 118.92 (CH), 109.49 (CH), 52.12 (CH_3) and 9.52 (CH_3); *m/z* 265 (M^+, 72%), 232 (20), 204 (36), 123 (61) and 77 (100).

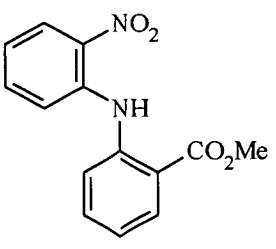
Synthesis of Methyl 2-benzoimidazol-1-ylbenzoate.

This compound was synthesised by a literature method which involved three steps.[131, 132]

i/ Synthesis of Methyl 2-(2-nitrophenylamino)benzoate.

2-Nitroaniline (4.45 g, 0.032 mol), methyl 2-iodobenzoate (8.44 g, 0.032 mol), potassium carbonate (4.45 g, 0.032 mol) and copper bronze (0.3 g) were heated under reflux at 160 °C for 6 h under a nitrogen atmosphere. After cooling, the reaction mixture was extracted using hot chloroform (2 × 100 cm^3) and filtered. The filtrate was concentrated under reduced pressure and the resulting solid was recrystallised from acetone.

Methyl 2-(2-nitrophenylamino)benzoate 413.



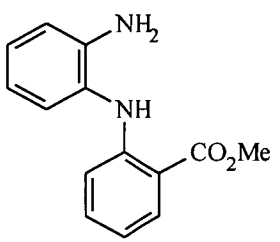
(75%) mp 151 – 152 ° C, [lit.,[131] 152 – 153 °C]; δ_H (250 MHz) 11.12 (1H, br), 6.89 – 8.15 (8H, m) and 3.95 (3H, s); δ_C (63 MHz) 167.37 (quat), 142.17 (quat), 138.94 (quat), 137.22 (quat), 134 56 (CH), 133.27 (CH), 131.93 (CH), 126.54 (CH), 121.68 (CH), 119.78 (CH), 118.88 (CH), 118.52 (quat), 118.45 (CH) and 52.23 (CH_3).

ii/ Synthesis of Methyl 2-(2-aminophenylamino)benzoate.

The nitro ester (5.0 g, 18.4 mmol) was heated under reflux in methanol (350 cm^3) in the presence of palladium-on-charcoal catalyst (5%, 0.25 g) under a nitrogen

atmosphere. A solution of hydrazine hydrate (4.6 g, 92 mmol) in methanol (10 cm^3) was added gradually over 15 min and then heated for a further 4 h. The resultant solution was filtered and the filtrate concentrated under reduced pressure to give a solid which was recrystallised from methanol.

Methyl 2-(2-aminophenylamino)benzoate 414.

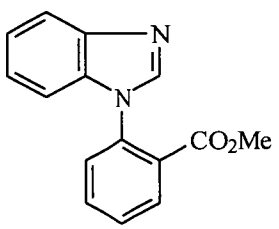


(90%) mp 100 – 101 °C, [lit.,[131] 101 – 102 °C]; δ_H (250 MHz) 8.97 (1H, br), 6.61 – 7.98 (8H, m), 3.91 (3H, s) and 3.75 (2H, br); δ_C (63 MHz) 168.93 (quat), 149.35 (quat), 143.21 (quat), 134.26 (CH), 131.25 (CH), 127.61 (CH), 127.00 (CH), 125.73 (quat), 118.66 (CH), 116.23 (CH), 115.76 (CH), 113.61 (CH), 110.80 (quat) and 51.59 (CH_3).

iii/ Synthesis of Methyl 2-benzoimidazol-1-ylbenzoate.

Methyl 2-(2-Aminophenylamino)benzoate (1 mmol) and formic acid (10 cm^3) were heated for 2 h at 130 °C. The solution was cooled and ether was added. The solution was extracted with dil HCl (3 × 50 cm^3). The aqueous layer was made alkaline with aqueous potassium carbonate solution and then extracted with ether (3 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

Methyl 2-benzoimidazol-1-ylbenzoate 411.

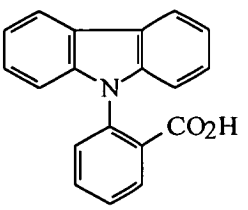


(60%) mp 88 – 89 °C (from toluene) [lit.,[132] 88°C] δ_H (250 MHz) 8.08 (1H, ddd, ^3J 7.7, ^4J, 1.7, ^5J 0.3), 8.00 (1H, br), 7.85 (1H, br d, ^3J 6.9), 7.70 (1H, td, ^3J 7.5, ^4J 1.6), 7.58 (1H, td, ^3J 7.7, ^{4}J 1.4), 7.14 – 7.48 (4H, m) and 3.46 (3H, s); δ_C (63 MHz) 165.63 (quat), 143.32 (CH), 135.08 (quat), 133.19 (CH), 131.82 (CH), 128.95 (CH), 128.28 (CH), 123.46 (CH), 122.35 (CH), 120.22 (CH), 109.68 (CH) and 52.29 (CH_3) [3 quats missing]; *m/z* 252 (M^+, 100%), 220 (55), 192 (39), 166 (15), 140 (13), 92 (32), 83 (15) and 76 (22).

10.3 Synthesis of carboxylic acids.

The methyl ester (1mmol) was dissolved in methanol (5 cm^3) and 1M NaOH (5 cm^3) was added. The solution was heated to reflux for 3 h. The methanol was removed under reduced pressure. The aqueous solution was acidified and then extracted with ether (3 × 50 cm^3). The organics were washed (2 × 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

2-Carbazol-9-ylbenzoic acid 431.



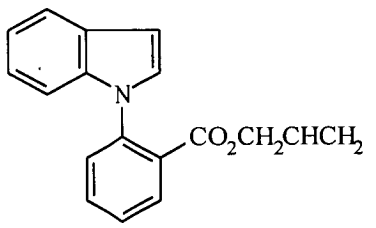
(20%) mp 182 - 183 °C [lit.,[166] 184 °C] δ_H (250 MHz) 9.39 (1H, br), 8.07 - 8.17 (3H, m), 7.76 (1H, td, ^3J 7.7, ^4J 1.5), 7.55 (2H, ddd, ^3J 8.0, 7.9, ^4J 1.1), 7.28 - 7.39 (4H, m) and 7.10 (2H, d, ^3J 8.0); δ_C (63 MHz) 170.76 (quat), 141.97 (2 × quat), 137.85 (quat), 134.49 (CH), 132.98 (CH), 130.75 (CH), 129.73 (quat), 128.77 (CH), 126.58 (2 × CH), 123.84 (2 × quat), 120.73 (2 × CH), 120.26 (2 × CH) and 109.85 (2 × CH).

10.4 Synthesis of allyl esters.

Method 1

Indole (2.95 g, 25 mmol), *o*-iodobenzoic acid (6.20 g, 25 mmol), anhydrous potassium carbonate (7.00 g, 50 mmol) was heated to reflux overnight in DMF (50 cm^3). The mixture was allowed to cool. Potassium carbonate (7.00 g, 50 mmol) and allyl bromide (3.60 g, 30 mmol) were added and the mixture was allowed to stir overnight at room temperature. The mixture was added to water (100 cm^3) and extracted with ether (3 × 100 cm^3). The combined organics were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was subjected to dry flash chromatography on silica using hexane as eluant. (It should be noted that attempted isolation of the acid after the initial aryl coupling was not successful owing to its solubility and partition properties)

Allyl 2-indol-1-ylbenzoate 394.



(47%) bp 150 - 152 °C (2 Torr) (Found: M^+, 277.1091. $C_{18}H_{15}NO_2$ requires *M*, 277.1103); δ_H (250 MHz) 8.03 (1H, m), 7.47 - 7.72 (4H, m), 7.12 - 7.24 (4H, m), 6.70 (1H, d, ^3J 3.2), 5.38 (1H, m), 4.96 - 5.04 (2H, m) and 4.34 - 4.37 (2H, m); δ_C (63 MHz) 165.97 (quat), 138.52 (quat), 137.15 (quat), 132.71 (CH), 131.18 (CH), 131.10 (CH), 128.96 (quat), 128.65 (CH), 128.52 (quat), 128.39 (CH), 127.52 (CH), 122.14 (CH), 120.80 (CH), 119.98 (CH), 118.27 (CH_2), 109.64 (CH), 103.12 (CH) and 65.90 (CH_2); *m/z* 277 (M^+, 8%), 231 (13), 193 (6), 177 (100), 90 (43) and 76 (6).

NOTE:- When carbazole and the 2- and 3-methylindoles were used, unreacted starting materials were recovered with no desired products. Using *o*-fluorobenzoic acid gave the same results.

Method 2.

This method of a 2 step, one pot, (hydrolysis/esterification process) was used.

The methyl ester (3 mmol) was dissolved in methanol (40 cm^3) and 1M NaOH (10 cm^3) was added. The mixture was heated to reflux for 2 h and then the solvents were removed under reduced pressure. Allyl bromide (3 mmol), potassium carbonate (3 mmol) and DMF (30 cm^3) were added and the mixture was heated to 60 °C overnight, allowed to cool and added to water (100 cm^3). This was extracted with ether (3 × 100 cm^3), the combined organics were washed (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was subjected to dry flash chromatography on silica using hexane : ethyl acetate as eluant.

[This method of a 2-step; hydrolysis, then esterification, reaction taking place in one pot was adopted for the following reasons.

1/ methyl 2-carbazol-9-ylbenzoate was subjected to two sets of ester exchange conditions and in each case, starting material was recovered from the reaction mixture.

These conditions were-

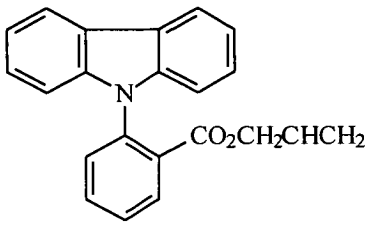
A/ The ester (1 mmol) was dissolved in allyl alcohol (30 cm^3) and Hunig's base (0.5 mmol) was added. The solution was heated to reflux overnight. The solvent was removed under reduced pressure and the residue subjected to ^1H NMR spectroscopy.

B/ Sodium metal (100 mg) was dissolved in allyl alcohol (30 cm^3), under dry nitrogen. The ester (1 mmol) was added and the solution heated to reflux overnight. The solvent was removed under reduced pressure and water (20 cm^3) was added. The solution was acidified with 1M HCl and then extracted with ether (3 × 100 cm^3), washed with water (2 ×. 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

2/ Ester exchange reactions on methyl benzoate, using Method B showed that hydrolysis was taking place rather than the ester exchange. Therefore a second alkylation step was needed.

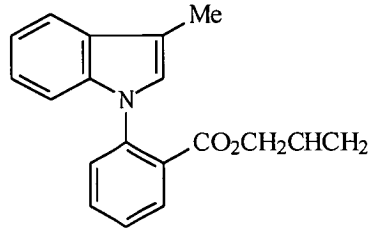
When methyl 2-carbazol-9-ylbenzoate was used as a substrate, the allylation reaction failed at room temperature (standard K_2CO_3/DMF alkylation conditions). However when heated at 60 °C overnight, compound **402** was obtained.]

Allyl 2-carbazol-9-ylbenzoate 402.



(80%) mp 71 – 72 °C (from hexane) (Found: C, 79.85; H, 5.2; N, 4.2. $C_{22}H_{17}NO_2.0.2H_2O$ requires C, 79.85, H, 5.15, N, 4.25%); (Found: M^+, 327.1253. $C_{22}H_{17}NO_2$ requires *M*, 327.1259); δ_H (250 MHz) 8.12 - 8.17 (3H, m), 7.58 - 7.80 (3H, m), 7.24 - 7.42 (4H, m), 7.15 (2H, dt, ^3J 8.0, ^4J 0.9), 5.07 (1H, m), 4.70 - 4.85 (2H, m) and 4.09 - 4.12 (2H, m); δ_C (63 MHz) 165.67 (quat), 141.48 (2 × quat), 136.71 (quat), 133.28 (CH), 131.94 (CH), 130.70 (CH), 130.23 (quat), 130.07 (CH), 128.24 (CH), 125.81 (2 × CH), 123.19 (2 × quat), 120.13 (2 × CH), 119.65 (2 × CH), 118.01 (CH_2), 109.19 (2 × CH) and 65.76 (CH_2); *m/z* 327 (M^+, 17%), 241 (7), 169 (12), 151 (89), 127 (38), 99 (15), 81 (45), and 41 (100).

Allyl 2-(3-methylindol-1-yl)benzoate 409.



(77%) bp 220 - 221 °C (2 Torr) (Found: M^+, 291.1260. $C_{19}H_{17}NO_2$ requires *M*, 291.1259); δ_H (250 MHz) 8.01 (1H, m), 7.45 – 7.66 (4H, m), 7.03 – 7.24 (4H, m), 5.44 (1H, m), 4.99 – 5.07 (2H, m), 4.36 – 4.40 (2H, m) and 2.43 (3H, s); δ_C (63 MHz) 166.18 (quat), 138.63 (quat), 137.23 (quat), 132.56 (CH), 131.12 (CH), 131.03 (CH), 129.06 (quat), 128.70 (quat), 128.07 (CH), 126.98 (CH), 126.14 (CH), 122.08 (CH), 119.36 (CH), 118.84 (CH), 118.10 (CH_2), 112.32 (quat), 109.45 (CH), 65.80 (CH_2) and 9.44 (CH_3); *m/z* 291 (M^+, 2%), 269 (11), 241 (14), 159 (13), 136 (26), 105 (27), 91 (30), 77 (33) and 41 (100).

10.5 Pyrolysis of methyl esters.

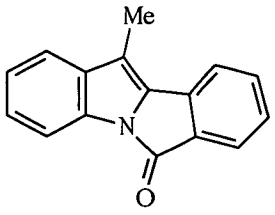
The appropriate derivative was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent to enable

removal from the trap. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets.

Methyl 2-(3-methylindol-1-yl)benzoate 408.

[T_f 950 °C, T_i 125 - 150 °C, P 0.0034 Torr, t_m 30 min, m_a 250 mg]

Pyrolysis produced 11-methylisoindolo[2,1-*a*]indol-6-one **418** after dry flash chromatography on silica using hexane : ethyl acetate as eluant.

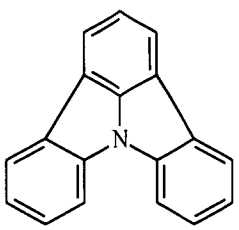


(90 mg, 43%) mp 160 - 161 °C (Found: C, 81.65; H, 4.65; N, 6.2. $C_{16}H_{11}NO.0.1H_2O$ requires C, 81.75, H, 4.7, N, 5.95%); (Found: M^+, 233.0840. $C_{16}H_{11}NO$ requires M, 233.0841); δ_H (250 MHz) 7.11 – 7.78 (8H, m) and 2.29 (3H, s); δ_C (63 MHz) 161.95 (quat), 135.50 (quat), 134.65 (quat), 134.26 (quat), 133.59 (quat), 133.22 (quat), 133.14 (CH), 127.73 (CH), 126.19 (CH), 124.89 (CH), 123.33 (CH), 120.84 (CH), 119.91 (CH), 115.15 (quat), 112.96 (CH) and 9.18 (CH_3); *m/z* 265 (M^+, 100%), 232 (23), 219 (25), 204 (42), 179 (15), 130 (49), 117 (57) and 77 (37).

Methyl 2-carbazol-9-ylbenzoate 401.

[T_f 950 °C (and silica tubes), T_i 140 - 160 °C, P 0.0042 Torr, t_m 60 min, m_a 0.35 g]

Pyrolysis produced indolo[3,3,1-*jk*]carbazole **398** after dry flash chromatography on silica using hexane : ethyl acetate as eluant

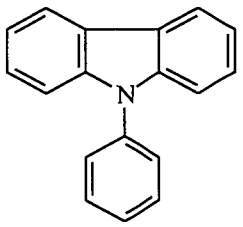


(30%) mp 135 – 136 °C [lit.,[117] 136.5 – 138.5 °C] δ_H (250 MHz) 8.13 – 8.18 (2H, m), 8.06 (2H, d, ^3J 7.4), 7.90 – 7.94 (2H, m), 7.60 (1H, t, ^3J 7.4), 5.57 (2H, dt, ^3J 8.0, ^4J 1.2) and 7.37 (2H, dt, ^3J 7.6, ^4J, 1.0); δ_C (63 MHz) 143.53 (quat), 138.48 (2 × quat), 129.83 (2 × quat), 126.48 (2 × CH), 122.94 (2 × CH), 122.62 (CH), 121.46 (2 × CH), 119.19 (2 × CH), 118.25 (2 × quat) and 111.96 (2 × CH); *m/z* 241 (M^+, 100%), 213 (8), 121 (31) and 94 (11).

10.6 Pyrolysis of carboxylic acids.

Pyrolysis of 2-Carbazol-9-ylbenzoic acid.

[T_f 850 °C T_i 140 - 160 °C, P 0.0042 Torr, t_m 60 min, m_a 0.35 g]



Pyrolysis produced 9-phenylcarbazole **432** (39%) mp 95 - 96 °C [lit.,[81] 96 °C] δ_H (250 MHz) 8.20 - 7.25 (2H, m) and 7.35 - 7.70 (11H, m); δ_C (90 MHz) 141.40 (2 × quat), 130.22 (quat), 130.31 (2 × CH), 127.89 (CH), 127.62 (2 × CH), 126.38 (2 × CH), 123.85 (2 × quat), 120.75 (2 × CH), 120.36 (2 × CH) and 110.23 (2 × CH).

Pyrolysis of [*O*-^{2}H]1-naphthoic acid under a D_2O stream.

[T_f 950 °C, T_i 160 - 180 °C, P 0.0013 Torr, t_m 30 min, m_a 0.8 g]

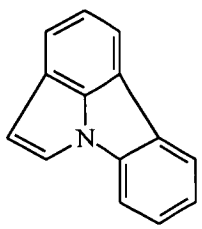
1-Naphthoic acid (100 mg) was dissolved in MeOD (5 cm^3). The [^{2}H]methanol was removed under reduced pressure and the resulting solid was pyrolysed under a D_2O stream. The pyrolysate was dissolved in $CHCl_3$ and a deuterium NMR spectrum was obtained. This showed no signals due to the deuterium.

10.7 Pyrolysis of allyl esters.

Allyl 2-indol-1-ylbenzoate.

[T_f 950 °C, T_i 160 - 180 °C, P 0.0013 Torr, t_m 30 min, m_a 0.8 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole **361** after dry flash chromatography on silica using hexane as eluant.

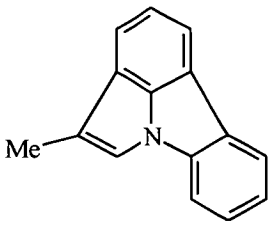


(0.23 g, 42%) mp 88 - 89 °C [lit.,[118] 89 - 90 °C] NMR data as before.

Allyl 2-(3-methylindol-1-yl)benzoate.

[T_f 950 °C, T_i 120 - 125 °C, P 0.0012 Torr, t_m 45 min, m_a 0.5 g]

Pyrolysis produced 4-methylpyrrolo[3,2,1-*jk*]carbazole **400** after dry flash chromatography on silica using hexane as eluant.

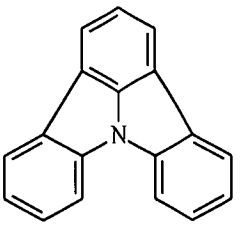


(100 mg, 28%) mp 58 - 59 °C (from hexane) (Found: M^+, 205.0893. $C_{15}H_{11}N$ requires *M*, 205.0892) δ_H (250 MHz) 8.07 (1H, ddd, ^3J 7.0, ^4J 1.3, ^5J 0.7), 7.92 (1H, d, ^3J 7.1), 7.77 (1H, d, ^3J 7.1), 7.59 (1H, ddd, ^3J 7.5, ^4J 1.2, ^5J 0.7), 7.51 (1H, t, ^3J 7.1), 7.42 - 7.54 (2H, m), 7.30 (1H, td, ^3J 7.5, ^4J 1.1) and 2.53 (3H, s); δ_C (63 MHz) 141.07 (quat), 139.38 (quat), 130.19 (quat), 126.40 (quat), 126.30 (CH), 122.89 (CH), 122.63 (CH), 121.35 (CH), 120.51 (quat), 119.70 (CH), 119.49 (CH), 118.80 (quat), 117.23 (CH), 110.92 (CH) and 11.08 (CH_3); *m/z* 204 (M^+, 100%), 191 (33), 176 (17), 151 (12), 102 (40), 88 (17) and 75 (15).

Allyl 2-carbazol-9-ylbenzoate

[T_f 950 °C, T_i 120 - 140 °C, *P* 0.0012 Torr, t_m 45 min, m_a 1.8 g]

Pyrolysis produced indolo[3,3,1-*jk*]carbazole **398** after dry flash chromatography on silica using hexane as eluant.



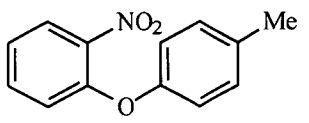
(0.8 g, 60%) mp 135 – 136 °C [lit.,[117] 136.5 – 138.5 °C] NMR data as before.

E. Synthesis and Pyrolysis of aromatic nitro compounds.

11.1 Synthesis of nitrophenyl ethers.

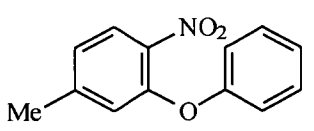
A halonitro compound (19 mmol), a hydroxy compound (19 mmol) and potassium hydroxide (1.06 g, 19 mmol) were heated overnight at 95 °C in DMSO (30 cm^3), under dry nitrogen. The cooled solution was added to water (100 cm^3) and extracted with ether (2 × 100 cm^3). The combined organics were washed with water (2 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The halonitro compound and hydroxy compound used are reported.

1-(4-methylphenoxy)-2-nitrobenzene 453a.



[*o*-chloronitrobenzene and *p*-cresol] (63%) mp 48 - 49 °C [lit., [167] 49 °C] δ_H (250 MHz) 7.91 (1H, dd, ^3J 8.3, ^4J 1.8), 7.45 (1H, m), 7.11 – 7.19 (2H, m), 6.92 – 6.98 (4H, m) and 2.34 (3H, s); δ_C (63 MHz) 153.09 (quat), 151.19 (quat), 134.28 (quat), 133.91 (CH), 130.42 (2 × CH), 125.53 (CH), 122.48 (CH), 119.64 (CH), 119.28 (2 × CH) and 20.63 (CH_3); [one quat missing].

(5-methyl-2-nitrophenyl)phenyl ether 457.



[3-fluoro-4-nitrotoluene and phenol] (59%) mp 62 - 63 °C [lit., [167] 63.5 - 64.5 °C] δ_H (250 MHz) 7.88 (1H, d, ^3J 8.4) and 6.79 – 7.41 (7H, m) and 2.32 (3H, s); δ_C (63 MHz) 155.74 (quat), 150.57 (quat), 145.92 (quat), 130.13 (quat), 129.86 (2 × CH), 125.69 (CH), 124.22 (CH), 123.85 (CH), 120.79 (CH), 118.93 (2 × CH) and 21.45 (CH_3).

11.2 Pyrolysis of nitrophenyl ethers.

The appropriate derivative was sublimed, under vacuum, through the furnace tube and the product(s) were collected in a trap cooled by liquid nitrogen. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent to enable removal from the trap. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets. [yields from ^{1}H NMR]

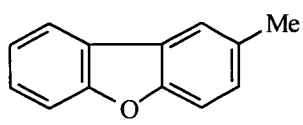
1-(4-methylphenoxy)-2-nitrobenzene

[T_f 650 °C, T_i 120 - 130 °C, P 0.016 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 1-(4-methylphenoxy)-2-nitrobenzene **453a** (100% recovery of starting materials)

[T_f 700 °C, T_i 120 - 130 °C, P 0.012 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 1-(4-methylphenoxy)-2-nitrobenzene **453a** (47%) and 2-methyldibenzofuran[168] **455** (53%)



δ_H (250 MHz) 7.23 – 7.96 (7H, m) and 2.51 (3H, s); δ_C (63 MHz) 156.33 (quat), 154.35 (quat), 132.05 (quat), 128.07 (CH), 127.03 (quat), 126.79 (CH), 124.05 (quat), 122.38 (CH), 120.49 (CH), 120.39 (CH), 111.49 (CH), 111.01 (CH), and 21.21 (CH_3).

[T_f 750 °C, T_i 120 - 130 °C, P 0.012 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 1-(4-methylphenoxy)-2-nitrobenzene **453a** (24%) and 2-methyldibenzofuran **455** (76%).

[T_f 850 °C, T_i 120 - 130 °C, P 0.017 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 1-(4-methylphenoxy)-2-nitrobenzene **453a** (2%) and 2-methyldibenzofuran **455** (98%)

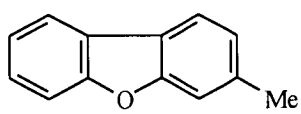
[T_f 950 °C, T_i 120 - 130 °C, P 0.017 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 2-methyldibenzofuran **455** (100%)

(5-methyl-2-nitrophenyl)phenyl ether

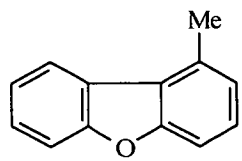
[T_f 850 °C, T_i 120 - 130 °C, P 0.014 Torr, t_m 30 min, m_a 80 mg]

Pyrolysis produced 3-methyldibenzofuran[126] **460** (75%)



δ_H (250 MHz) 7.96 – 8.00 (2H, m), 7.69 (2H, m), 7.39 – 7.59 (2H, m), 7.22 (1H, m) and 2.53 (3H, s); δ_C (63 MHz) 156.60 (quat), 156.15 (quat), 137.48 (quat), 126.35 (CH), 124.31 (quat), 123.77 (CH), 122.40 (CH), 121.59 (quat), 120.11 (CH), 119.97 (CH), 111.79 (CH), 111.38 (CH) and 21.70 (CH_3) and

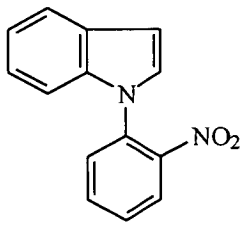
1-methyldibenzofuran[126] **461** (25 %) δ_H (250 MHz) 8.05 (1H, m), 7.38 – 7.59 (5H, m), 7.17 – 7.26 (1H, m) and 2.81 (3H, s); δ_C (63 MHz) 156.18 (quat), 156.08 (quat), 133.43 (quat), 126.79 (CH), 126.39 (CH), 124.83 (quat), 123.82 (CH), 122.48 (CH), 122.21 (CH), 111.38 (CH), 108.91 (CH) and 19.61 (CH_3).[one quat missing]



11.3 Synthesis of 1-(2-nitrophenyl)-heterocycles.

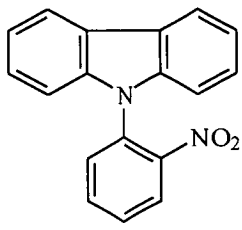
The appropriate heterocycle (10 mmol), potassium carbonate (10.2 mmol) and *o*-fluoronitrobenzene (10 mmol) was heated at 125 °C in DMF (30 cm^3). The cooled solution was added to water (100 cm^3). This was extracted using ether (3 × 100 cm^3). The combined organics were washed using water (3 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The period of heating and purification method is shown in each case.

1-(2-nitrophenyl)-indole 458a.



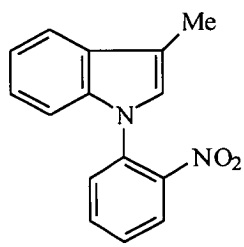
(8 h, 2.00 g, 84%) mp 81 – 82 °C [lit.,[127] 82 – 83 °C] δ_H (360 MHz) 8.03 (1H, m), 7.52 – 7.77 (4H, m), 7.09 – 7.23 (4H, m) and 6.74 (1H, dd, *J* 3.3, 0.7); δ_C (90 MHz) 146.72 (quat), 137.14 (quat), 134.16 (CH), 133.27 (quat), 130.20 (CH), 129.42 (quat), 128.82 (CH), 128.45 (CH), 125.95 (CH), 123.41 (CH), 121.79 (CH), 121.40 (CH), 109.94 (CH) and 105.46 (CH); *m/z* 238 (M^+, 74%), 193 (57), 191 (53), 180 (43), 117 (100), 90 (61) and 76 (18).

9-(2-nitrophenyl)-carbazole 458b.



(24 h, 2.60 g, 90%) mp 154 - 155 °C [lit.,[133] 156 °C]; δ_H (250 MHz) 8.12 - 8.17 (2H, m), 7.79 (1H, m), 7.60 - 7.67 (2H, m), 7.23 - 7.43 (5H, m) and 7.10 - 7.14 (2H, m); δ_C (63 MHz) 162.38 (quat), 147.11 (quat), 140.55 (2 × quat), 134.13 (CH), 131.18 (CH), 128.99 (CH), 126.15 (2 × CH), 123.76 (CH), 123.63 (2 × quat), 120.49 (2 × CH), 120.39 (2 × CH) and 108.88 (2 × CH); *m/z* 288 (M^+, 25%), 241 (16), 167 (100), 139 (10) and 84 (11).

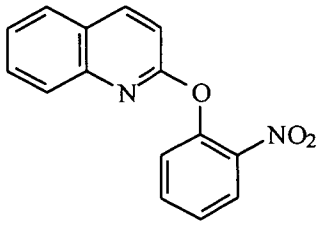
1-(2-nitrophenyl)-3-methylindole 458c.



(24 h, 1.63 g, 65%) mp 68 - 70 °C (from ethanol) (Found: M^+, 252.0899. $C_{15}H_{12}N_2O_2$ requires *M*, 252.0899); δ_H (250 MHz) 7.98 - 8.02 (1H, m), 7.46 - 7.72 (4H, m), 7.09 - 7.35 (3H, m), 6.94 (1H, s) and 2.39 (3H, s); δ_C (63 MHz) 145.90 (quat), 136.48 (CH), 133.44 (quat), 132.80 (quat), 129.43 (quat),

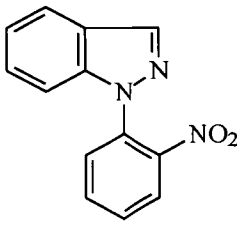
129.18 (CH), 127.54 (CH), 125.29 (CH), 125.03 (CH), 122.74 (CH), 120.21 (CH), 119.23 (CH), 114.22 (quat), 109.17 (CH) and 9.44 (CH_3); *m/z* 252 (M^+, 12%), 207 (8), 130 (100), 103 (10) and 77 (16).

2-(2-nitrophenoxy)quinoline 462.



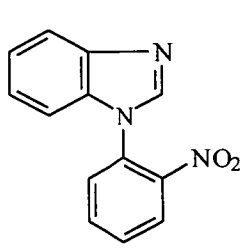
(24 h, 2.26 g, 85%) mp 110 – 111 °C (from ethanol) (Found: C, 67.5; H, 3.4; N, 9.95. $C_{15}H_{10}N_2O_3$ requires C, 67.65; H, 3.75; N, 10.5%); δ_H (250 MHz) 8.11 – 8.22 (2H, m), 7.40 – 7.82 (7H, m) and 7.27 (1H, d, ^3J 6.1); δ_C (63 MHz) 160.81 (quat), 147.00 (quat), 146.20 (quat), 143.32 (quat), 140.69 (CH), 134.85 (CH), 130.34 (CH), 128.15 (CH), 127.85 (CH), 126.37 (quat), 126.00 (CH), 125.89 (2 × CH), 125.53 (CH) and 112.76 (CH); *m/z* 266 (M^+, 6%), 220 (100), 191 (14), 165 (6), 128 (32), 101 (26) and 77 (17).

1-(2-nitrophenyl)-indazole 458d.



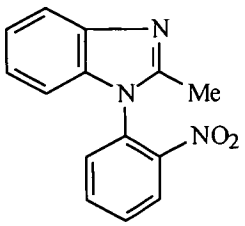
(8 h, 57%, recrystallised three times from toluene) mp 151 – 152 °C [lit.,[147] 152 – 153 °C] δ_H (250 MHz) 8.22 (1H, s) and 7.22 – 8.03 (8H, m); δ_C (63 MHz) 142.85 (quat), 139.45 (quat), 136.89 (CH), 133.14 (CH), 132.72 (quat), 128.16 (CH), 127.66 (CH), 127.15 (CH), 125.53 (CH), 124.95 (quat), 122.02 (CH), 121.49 (CH) and 109.19 (CH); *m/z* 239 (M^+, 100%), 222 (86), 192 (54), 166 (49), 140 (37), 118 (63), 91 (50) and 77 (60).

1-(2-nitrophenyl)-benzimidazole 458e.



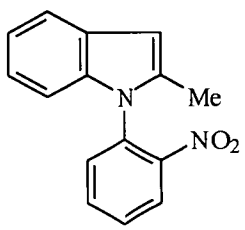
(8 h, 1.94 g, 81%) mp 80 - 81 °C [lit.,[127] 80 - 82 °C] δ_H (250 MHz) 8.14 (1H, dd, ^3J 8.0, ^4J 1.6), 8.01 (1H, s), 7.54 - 7.89 (4H, m) and 7.10 - 7.38 (3H, m); δ_C (63 MHz) 145.97 (quat), 143.23 (quat), 142.32 (CH), 134.17 (CH), 129.90 (CH), 129.62 (CH), 129.27 (quat), 125.84 (CH), 124.09 (CH), 123.07 (CH), 120.66 (CH) and 109.32 (CH) [one quat missing]; *m/z* 239 (M^+, 61%), 222 (7), 192 (23), 181 (60), 140 (17), 77 (20) and 43 (100).

1-(2-nitrophenyl)-2-methylbenzimidazole 458f.



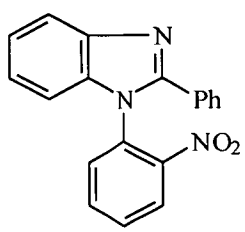
(8 h, 1.01 g, 40%) mp 110 - 111 °C (Found: C, 66.05; H, 4.25; N, 16.75. $C_{14}H_{11}N_3O_2$ requires C, 66.4; H, 4.35; N, 16.6%); δ_H (360 MHz) 8.21 (1H, dd, ^3J 8.1, ^4J 1.5), 7.87 (1H, td, ^3J 7.8, ^4J 1.6), 7.75 - 7.80 (2H, m), 7.54 (1H, dd, ^3J 7.8, ^4J 1.5), 7.18 - 7.32 (2H, m), 6.92 (1H, dd, ^3J 8.1, ^4J 1.1) and 2.47 (3H, s); δ_C (90 MHz) 152.04 (quat), 147.31 (quat), 143.23 (quat), 136.83 (quat), 134.87 (CH), 131.53 (CH), 131.05 (CH), 130.03 (quat), 126.35 (CH), 123.54 (CH), 123.23 (CH), 119.79 (CH), 109.43 (CH) and 14.47 (CH_3); *m/z* 253 (M^+, 57%), 236 (8), 206 (23), 181 (42), 132 (100), 104 (28), 91 (39) and 77 (40).

1-(2-nitrophenyl)-2-methylindole 458g.



(24 h, 0.87 g, 34%, dry flash chromatography on silica using hexane : ethyl acetate as eluant) mp 90 – 91 °C (from ethanol) (Found: C, 71.4; H, 4.6; N, 10.65. $C_{15}H_{12}N_2O_2$ requires C, 71.45; H, 4.75; N, 11.1%); (Found: M^+, 252.0898. $C_{15}H_{12}N_2O_2$ requires *M*, 252.0899); δ_H (250 MHz) 8.08 (1H, m), 7.45 – 7.81 (4H, m), 6.81 - 7.16 (3H, m), 6.46 (1H, s) and 2.24 (3H, s); δ_C (90 MHz) 148.46 (quat), 138.69 (quat), 137.65 (quat), 134.26 (CH), 132.38 (CH), 132.08 (quat), 129.94 (CH), 129.11 (quat), 125.83 (CH), 122.11 (CH), 121.04 (CH), 120.39 (CH), 109.50 (CH), 102.94 (CH) and 13.27 (CH_3); *m/z* 252 (M^+, 100%), 235 (41), 204 (82), 131 (86), 103 (27), 89 (16) and 77 (39).

1-(2-nitrophenyl)-2-phenylbenzimidazole 458h.



(24 h, 2.55 g, 81%) mp 158 – 159 °C (from ethanol) (Found: C, 71.6; H, 4.2; N, 13.25, $C_{19}H_{13}N_3O_2$ requires C, 72.4; H, 4.15; N, 13.35%); (Found: M^+, 315.1008. $C_{19}H_{13}N_3O_2$ requires *M*, 315.1008); δ_H (360 MHz) 8.11 (1H, m), 8.12 (1H, dd, ^3J 8.2, ^4J 1.6), 7.80 (1H, td, ^3J 7.6, ^4J 1.6), 7.70 (1H, m), 7.93 (1H, d, ^3J 8.0), 7.53 – 7.58 (2H, m), 7.22 – 7.47 (5H, m) and 7.10 (1H, d, ^3J 8.0); δ_C (90 MHz) 153.04 (quat), 146.57 (quat), 143.58 (quat), 136.95 (quat), 134.91 (CH), 131.37 (CH), 131.11 (quat), 130.54 (CH), 130.39 (CH), 129.54 (2 × CH), 129.05 (2 × CH), 128.78 (quat), 126.47 (CH), 124.39 (CH), 123.95 (CH), 120.63 (CH) and

110.01 (CH); *m/z* 315 (M^+, 12%), 260 (11), 238 (4), 194 (100), 139 (14), 122 (50), 105 (33) and 77 (35).

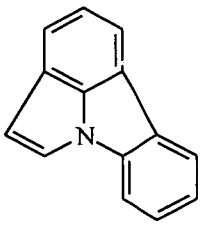
11.4 Pyrolysis of *N*-(2-nitrophenyl)-heterocycles.

Small-scale pyrolysis reactions of these derivatives were carried out using a U-tube trap as previously described. However, when these reactions were repeated on a large (0.5 g and above) scale, the product decomposed in the U-tube trap. It is noted that attempts to cool this sidearm of the U-tube using dry ice, caused the product to collect inside the furnace tube, where it decomposed thermally. An alternative trapping system was designed where the appropriate derivative was sublimed, under vacuum, through the furnace tube, and the product(s) were collected in a cold finger trap which was at the exit point of the furnace and was cooled with dry-ice and acetone. (The joint between this trap and the furnace tube was pushed into the furnace to ensure that the majority of the product solidified on the cold finger and not on the sidearm, so that decomposition of the product was minimised). The cold-finger trap had a U-tube connected in series which was cooled with liquid nitrogen to trap the nitrogen oxide co-product. Upon completion of the pyrolysis, nitrogen gas was released through the system, which was then taken apart before the U-tube could warm to room temperature (This prevented the product in the cold-finger trap coming into contact with the reactive nitrogen gases again), and the U-tube was placed in a fume-cupboard to allow it to warm to room temperature. The dry ice/acetone mixture was poured from the cold-finger which was then immediately dismantled. Care was taken to avoid the product coming into contact with any greased joints. The product was quickly washed off using dichloromethane to prevent water from condensing on it. The product was then subjected to normal purification procedures. The following derivatives were pyrolysed, with the pyrolysis parameters given in brackets.

1-(2-nitrophenyl)-indole

[T_f 850 °C, T_i 150 - 180 °C, P 0.013 Torr, t_m 30 min, m_a 0.8 g]

Pyrolysis produced pyrrolo[3,2,1-*jk*]carbazole **361** after dry flash chromatography on silica using hexane as eluant.

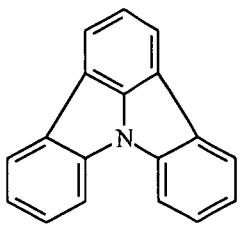


(0.21 g, 33%) mp 88 - 89 °C [lit.,[118] 89 - 90 °C] NMR data as previously described.

9-(2-nitrophenyl)-carbazole

[T_f 850 °C, T_i 140 - 160 °C, P 0.027 Torr, t_m 20 min, m_a 0.5 g]

Pyrolysis produced indolo[3,2,1-*jk*]carbazole **398** (0.20 g, 48 %) after dry flash chromatography on silica using hexane as eluant.

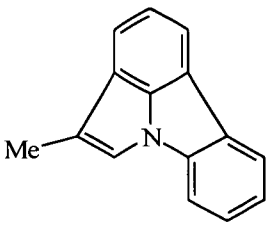


mp 135 – 136 °C [lit.,[117] 136.5 – 138.5 °C] NMR data as previously described.

1-(2-nitrophenyl)-3-methylindole

[T_f 850 °C, T_i 150 - 180 °C, P 0.013 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 4-methylpyrrolo[3,2,1-*jk*]carbazole **400**



(27%) δ_H (250 MHz) 6.87 - 8.33 (8H, m) and 2.54 (3H, s); δ_C (63 MHz) 140.97 (quat), 139.29 (quat), 130.10 (quat), 126.36 (quat), 126.26 (CH), 122.83 (CH), 122.60 (CH), 121.30 (CH), 120.44 (quat), 119.66 (CH), 119.42 (CH), 118.72 (quat), 117.19 (CH), 110.88 (CH) and 11.01 (CH_3); *m/z* 204 (M^+, 100%), 191 (91), 151 (6), 102 (22), 89 (10) and 75 (11). (This reaction was carried out on a small scale and the yield was obtained by introduction of a known amount of cyclohexane to the sample and subsequent proton NMR experiments. Large scale pyrolysis experiments on this compound were not clean and attempts to separate components using dry flash chromatography proved to be unsuccessful)

2-(2-nitrophenoxy)quinoline.

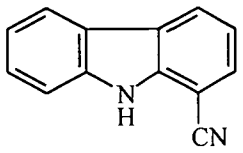
[T_f 850 °C, T_i 160 - 180 °C, P 0.0027 Torr, t_m 30 min, m_a 100 mg]

Examination of the pyrolysate by ^{1}H NMR spectroscopy showed no identifiable products.

1-(2-nitrophenyl)-indazole

[T_f 850 °C, T_i 250 - 270 °C, P 0.013 Torr, t_m 30 min, m_a 0.35 g]

Pyrolysis produced 1-cyanocarbazole **467** after dry flash chromatography on silica using hexane : ethyl acetate as eluant.

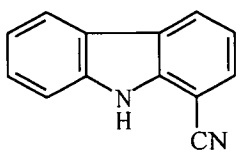


(0.16 g, 57%) mp 189 - 190 [lit.,[154] 188 - 189°C] δ_H (250 MHz) 9.00 (1H, br), 8.27 (1H, dt, ^3J 7.7, ^4J 1.1), 8.08 (1H, ddd, ^3J 6.9, ^4J 1.7, ^5J 0.9), 7.68 (1H, dd, ^3J 7.7, ^4J 1.1), 7.45 - 7.57 (2H, m), 7.29 (1H, dd, ^3J 6.5, ^4J 1.4) and 7.25 (1H, t, ^3J 7.7); δ_C (90 MHz) 140.49 (quat), 139.38 (quat), 129.06 (CH), 127.18 (CH), 125.07 (CH), 124.23 (quat), 122.42 (quat), 120.55 (2 × CH), 119.18 (CH), 117.25 (quat), 111.20 (CH) and 93.50 (quat); *m/z* 192 (M^+, 100%), 164 (15), 138 (5) and 96 (7).

1-(2-nitrophenyl)-benzimidazole

[T_f 850 °C, T_i 160 - 180 °C, P 0.0034 Torr, t_m 20 min, m_a 0.5 g]

Pyrolysis produced 1-cyanocarbazole after dry flash chromatography on silica using hexane : ethyl acetate as eluant.

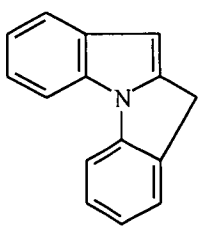


(0.26 g, 64%) mp 189 - 190 [lit.,[xx] 188 - 189°C]; NMR data as above.

1-(2-nitrophenyl)-2-methylindole

[T_f 850 °C, T_i 150 - 180 °C, P 0.015 Torr, t_m 30 min, m_a 50 mg]

Pyrolysis produced 10*H*-indolo[1,2-*a*]indole **482**

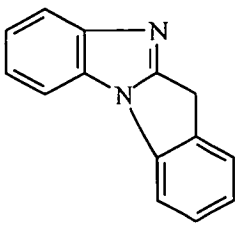


(51%) mp 80 - 81 °C (Found: M^+, 205.0888. $C_{15}H_{11}N$ requires M, 205.0892) δ_H (250 MHz) 7.83 (1H, ddd, ^3J 8.0, ^4J 1.8, ^5J 0.8), 7.14 – 7.73 (7H, m), 6.53 (1H, td, ^3J 1.7, ^4J 0.8) and 4.08 (2H, s); δ_C (63 MHz) 142.71 (quat), 141.98 (quat), 134.21 (quat), 133.70 (quat), 131.10 (quat), 128.24 (CH), 126.23 (CH), 122.81 (CH), 121.94 (CH), 121.37 (CH), 120.82 (CH), 111.05 (CH), 110.75 (CH), 96.71 (CH) and 29.47 (CH_2); *m/z* 205 (M^+, 100%), 191 (13) and 102 (26).* (Purification of this compound proved difficult with distillation and chromatography causing decomposition of this compound. A small scale sublimation was used to get a sample pure enough for characterisation purposes)

1-(2-nitrophenyl)-2-methylbenzimidazole

[T_f 850 °C, T_i 200 - 220 °C, P 0.016 Torr, t_m 30 min, m_a 0.1 g]

Pyrolysis produced 10*H*-4b,9-diaza-indeno[1,2-*a*]indene **468**



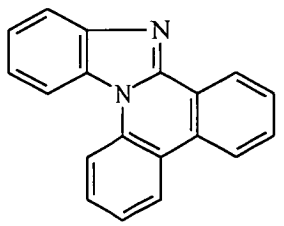
(49%) mp 162 – 163 °C (Found: M^+, 206.0849. $C_{14}H_{10}N_2$ requires *M*, 206.0849); δ_H (250 MHz) 7.22 - 7.86 (7H, m), 7.15 (1H, td, ^3J 7.5, ^4J 1.0) and 4.08 (2H, s); δ_C (90 MHz) 159.41 (quat), 147.87 (quat), 139.47 (quat), 132.46 (quat), 129.83 (quat), 128.59 (CH), 126.50 (CH), 124.55 (CH), 123.35 (CH), 123.11 (CH), 120.36 (CH), 111.17 (CH), 110.86 (CH) and 29.39 (CH_2); *m/z* 206 (M^+, 100 %), 179 (6), 128 (2), 103 (20) and 77 (11).* (as above)

1-(2-nitrophenyl)-2-phenylbenzimidazole

[T_f 850 °C, T_i 250 - 270 °C, P 0.022 Torr, t_m 50 min, m_a 0.8 g]

Pyrolysis produced benzo[4,5]imidazo[1,2-*f*]phenanthridine **450** after dry flash chromatography on silica using hexane : ethyl acetate as eluant.

(0.26 g, 38%) mp 154 °C [lit.,[143] 155 °C] δ_H (250 MHz) 8.92 (1H, dd, ^3J 7.2, ^4J 2.0), 8.60 (1H, dd, ^3J 8.4, ^4J 0.8), 8.52 (1H, dd, ^3J 8.1, ^4J 1.4), 8.37 - 8.44 (2H, m), 8.09 (1H, dd, ^3J 6.4, ^4J 1.8), 7.68 - 7.81 (3H, m) and 7.47 - 7.59 (3H, m); δ_C (90 MHz) 147.92 (quat), 144.93 (quat), 134.81 (quat), 132.28 (quat), 130.83 (CH), 129.90 (quat), 129.56 (CH), 129.03 (CH), 126.44 (CH), 124.83 (CH), 124.60 (CH), 124.53 (CH), 123.84 (quat), 123.33 (CH), 122.67 (CH), 122.09 (quat), 120.76 (CH), 116.40 (CH) and 114.33 (CH).

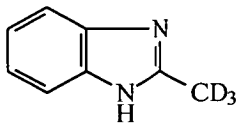


11.5 Synthesis of labelled precursors.

i/ Synthesis of 2-[$^2H_3$]-methylbenzimidazole

o-Phenylenediamine (0.5 g, 4.6 mmol) was heated for 2 h at 140 °C in [^{2}H]acetic acid (1.00 g, 15 mmol). The solution was allowed to cool and made alkaline with 1M NaOH. The crude benzimidazole was filtered off and recrystallised from ethanol.

2-[$^2H_3$]-methylbenzimidazole

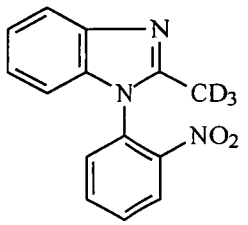


(42%) δ_H (250 MHz) 7.55 - 7.60 (2H, m) and 7.23 - 7.28 (2H, m); *m/z* 235 (M^+, 100%), 132 (33), 93 (10), 78 (7) and 64 (32).

Synthesis of 1-(2-nitrophenyl)-2-[$^2H_3$]-methylbenzimidazole

The benzimidazole (0.5 mmol), potassium carbonate (0.55 mmol) and *o*-fluoronitrobenzene (0.5 mmol) were heated at 125 °C in DMF (30 cm^3) for 24 h. The cooled solution was added to water (100 cm^3). This was extracted using ether (3 × 100 cm^3). The combined organics were washed using water (3 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure.

1-(2-nitrophenyl)-2-[$^2H_3$]-methylbenzimidazole 472.



(33%) mp 110 – 111 °C (Found: C, 65.2; H, 4.05; N, 16.0. $C_{14}H_8D_3N_3O_2$ requires C, 65.6; H, 3.15; N, 16.4%) (Found: M^+, 256.1043. $C_{14}H_8D_3N_3O_2$ requires *M*, 256.1039); δ_H (250 MHz) 8.21 (1H, dd, ^3J 8.1, ^4J 1.6), 8.08 (1H, m), 7.52 – 7.91 (3H, m), 7.10 – 7.37 (2H, m) and 6.92 (1H, m); δ_C (63 MHz) 147.27 (quat), 143.20 (quat), 136.79 (quat), 136.79 (quat), 134.88 (CH), 131.52 (CH), 131.06 (CH), 130.01 (quat), 126.36 (CH), 123.54 (CH), 123.22 (CH), 119.77 (CH) and 109.41 (CH); *m/z* 256 (M^+, 8%), 205 (8), 166 (16), 142 (31), 111 (62), 83 (100) and 77 (29).

11.6Pyrolysis of labelled precursors.

The pyrolysis was carried out as before using a U-tube trap only.

1-(2-nitrophenyl)-2-[$^2H_3$]-methylbenzimidazole

[T_f 850 °C, T_i 200 °C, P 0.012 Torr, t_m 20 min, m_a 20 mg]

Pyrolysis produced deuteriated product, the structure of which is still under investigation. (see discussion section)

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